VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

Clinical Study Protocol

Title:	A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus
Clinical Protocol Number:	KOR-CHINA-301
Version Date:	29 March 2022
Version Number:	2.0
Prior Version/Amendments:	Version 1.0, 16 July 2021
Investigational Drug	Difelikefalin (CR845)
Co-ordinating Investigator:	Professor Li Zuo
Sponsor Contact:	PPD
Sponsor Address:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 St. Gallen CH-9014 Switzerland

SIGNATURE PAGE

Declaration of Sponsor

Title: A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus

Clinical Protocol Number: KOR-CHINA-301

Version/Amendment Number/Date: Version 2.0, 29 March 2022

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended.

PPD

30-Mar-2022 | 10:27:42 CEST

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Date (day month year)

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Declaration of Co-ordinating Investigator

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Signature of Co-ordinating Investigator Professor Li Zuo Director, Department of Nephrology, Peking University People's Hospital PPD 11 Xizhimennan Street, Xicheng District Beijing, 100044 China PPD	Date (day month year)

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Title: A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus

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I have read the attached protocol as specified on this page and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended, and applicable local regulations, and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children)
- my Sub-investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Vifor Pharma.

Signature by the Investigator on this Protocol Signature Page documents review, agreement, and approval of the requirements contained within this protocol.

Signature of Principal Investigator	Date (day month year)

Name, Title, Address, Telephone Number, and Email of Principal Investigator

SYNOPSIS

KOR-CHINA-301

Title:	A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Subjects with Moderate-to-Severe Pruritus
Short Title:	Phase 3 Study of Difelikefalin in Haemodialysis (HD) Chinese Subjects with Moderate-to-Severe Pruritus
Study Product(s):	Difelikefalin (CR845)
Study Population:	HD Chinese subjects with moderate-to-severe pruritus
Phase:	3
Sponsor:	Vifor Fresenius Medical Care Renal Pharma Ltd.
Protocol Number:	KOR-CHINA-301
Co-ordinating Investigator:	Professor Li Zuo, Peking University People's Hospital, Beijing, China
Objectives:	Primary Objective: • To evaluate the efficacy of difelikefalin 0.5 µg/kg compared to placebo in reducing the intensity of itch in HD Chinese subjects with moderate-to-severe pruritus. Secondary Objectives: • To evaluate the efficacy of difelikefalin 0.5 µg/kg compared to placebo in improving the itch-related quality of life (QoL) in HD Chinese subjects with moderate-to-severe pruritus. • To evaluate the safety of difelikefalin 0.5 µg/kg in HD Chinese subjects with moderate-to-severe pruritus.
Design:	This multicentre study consists of a double-blind, randomised, placebo-controlled, parallel group period, and an optional open-label extension period.
Duration:	Total study duration for a single subject is 31 to 32 weeks with a 4-week screening period (including a 7-day run-in period during the week prior to randomisation), a 12-week double-blind period, a 14-week open-label extension period (starting within 1 week after the end of the double-blind period), and a 1-week follow-up period (1 week to 10 days). For subjects not participating in the open-label extension period, the total study duration is 17 weeks.
Treatment:	**Investigational Products** 1. Test drug Difelikefalin solution (intravenous (IV) formulation) will be supplied in 2 R glass vials with an extractable volume of 1 ml of difelikefalin at a concentration of 50 µg/ml in 0.04 M isotonic acetate buffer, pH 4.5.

2. Comparator

A matching placebo (0.04 M isotonic acetate buffer, pH 4.5) will be supplied in 2 R glass vials with an extractable volume of 1 ml.

Dosage and Administration

1. Screening period

A 4-week period before entry into the double-blind period is defined as the screening period, during which subjects will receive no investigational product. Subjects will continuously use any conditionally permitted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period.

2. Double-blind period

In addition to the use of conditionally permitted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period, the investigational product will be injected into the venous line of the dialysis circuit at the end of each dialysis session for 12 weeks (3 times weekly, 36 times in total). The total dose of the investigational product will be determined based on the subject's prescription dry body weight (i.e., the target post-dialysis weight, as determined by the patient's nephrologist or dialysis unit) at the start day of the double-blind treatment period.

The total dose volume (ml) required from the investigational product vial should be calculated as follows: 0.01 × prescription dry body weight (kg), rounded to the nearest tenth (0.1 ml).

If any dialysis circuit trouble precludes injection through the dialysis circuit, the investigational product will be administered directly intravenously. If in exceptional cases an extra fourth dialysis session is required within the week, the investigational product will be administered (up to 4 times weekly); if only the extracorporeal ultrafiltration method is used at this fourth dialysis session, the investigational product will not be administered.

3. Open-label extension period

In addition to the use of conditionally permitted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period, difelikefalin will be injected into the venous line of the dialysis circuit at the end of each dialysis session for 14 weeks (3 times weekly; 42 times in total). Investigational treatment in the extension period will be started at Week 13 and will be given until Week 26 inclusive. The participation in the open-label extension period is optional.

4. Follow-up period

The follow-up period is defined as 1 week (1 week to 10 days) after last administration of difelikefalin (end of extension period or early discontinuation).

Concomitant Treatments

Subjects may continuously use any conditionally permitted concomitant medication used to treat symptoms of chronic renal failure or other comorbidities at the start of the screening period without changing its dosage and administration regimen whenever possible until the end of the follow-up period. The dosage and administration of any concomitant medication may be changed for safety reasons including adverse events (AEs). Any centrally acting

	concomitant drug should be used with caution due to possible central AEs that might confound the safety profile of difelikefalin. 5. Prohibited concomitant treatments Between the start of the screening period and the end of the follow-up period, use of the following drugs will be prohibited: • Other kappa opioid receptor (KOR) agonists, e.g., nalfurafine hydrochloride • Opioid antagonists: naloxone hydrochloride, eptazocine hydrobromide, naldemedine tosylate, etc., or mixed agonists-antagonists (e.g., buprenorphine and nalbuphine) • Investigational products other than difelikefalin 6. Conditionally permitted concomitant treatments Between the start of the screening period and the end of the follow-up period, subjects may use the drugs listed below that have been used before the screening period without changing their dosage and administration. However, treatment with these drugs should not be initiated during the same time window defined above. a) Drugs indicated for the treatment of itching (prescription/non-prescription) except prohibited concomitant medications b) Drugs to treat itching including traditional Chinese medications (prescription/non-prescription) except prohibited concomitant medications c) Moisturising drugs (prescription/non-prescription) d) Steroids Note: Local steroids, such as inhalants, nasal drops, ear drops, eye drops, and eye ointments, are allowed. e) Capsaicin (topical) f) Opioids g) Pregabalin, gabapentin h) Antidepressants, anxiolytics i) Drugs formulated with any of the drugs listed above Topical use of any prescription/non-prescription drugs listed in a) to e) above that are used to treat itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted (concomitant medications for local itching caused by insect stings, chilblains, contact dermatitis, etc. will not be restricted). The use of any combination products that contain ingredients indicated for itching but are not indicated itself for itching will not be restricted. 7. Prohibited concomitant therapies Between the start of the screening period and the end of the follow-up period, phototherapy to treat itching will be prohibited.

	HD Conditions Between the start of the screening period and the end of the follow-up period, the frequency of dialysis per week and the HD method may not be changed. Any temporary change in dialysis frequency or HD method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable. The HD conditions (duration of dialysis and dialyser) should not be changed whenever possible.
Inclusion Criteria:	**Double-blind Period** The double-blind period of this study will enrol HD subjects with pruritus who meet all the inclusion criteria and none of the exclusion criteria listed below. 1. Subject (or legally accepted representative) has provided written informed consent. Written informed consent must be provided before any study-specific procedures are performed including screening procedures. 2. Chinese subjects aged ≥18 to 85 years (inclusive) at the time of consent. 3. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements, including providing written responses to questionnaires. 4. Subjects with chronic kidney disease (CKD) on HD 3 times weekly for ≥12 weeks prior to the informed consent procedure (including the date of informed consent) who can continue HD without changing its frequency or method. Note 1: Any temporary change in dialysis frequency or method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable, from the date of informed consent until the end of the follow-up period. Subjects routinely on 4 dialyses a week will not be eligible. Note 2: Subjects receiving in-home HD may participate as long as they have switched to in-centre HD at least 2 weeks prior to screening and plan to remain on in-centre HD for the duration of the study. Note 3: Subjects receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible. 5. If female, is not pregnant, or nursing. 6. If female: a. Is surgically sterile; or b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or

	c. Has a negative serum pregnancy test within 7 days before first dose of investigational product and agrees to use acceptable contraceptive measures (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after the last dose of investigational product. Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to end-stage renal disease (ESRD) unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed. 7. If male, agrees not to donate sperm after the first dose of investigational product administration until 7 days after the last dose of investigational product, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of investigational product. Note: No restrictions are required for a vasectomised male, provided his vasectomy was performed ≥4 months prior to screening. 8. Subjects whose Numerical Rating Scale (NRS) score (Appendix 1) in the 7-days run-in period (7 days including the score recorded on the start day of treatment) meets both of the below: a. NRS scores have been recorded for at least 4 days through a 7-day run-in period. b. The mean value of the recorded scores is ≥5.0 (moderate-to-severe pruritus). 9. Subjects with a prescription dry body weight between 40 and 100 kg, inclusive. 10. Over the last 3 months prior to screening, has had at least 1 of the following: a. At least 2 single-pool Kt/V measurements ≥1.2 on different dialysis days b. At least 2 urea reduction ratio measurements ≥65% on different dialysis days c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days **Open-label Extension Period** Subjects meeting all of the following inclusion criteria at the end of Week 12 of the double-blind period will enter the extension period. Subjects not meeting these inclusion criteria will be withdrawn from the study and undergo the follow-up assessments. 11. Subjects not withdrawn during the double-blind period. 12. Subjects receiving at least 30 doses of the planned 36 doses of investigational product during the double-blind period. 13. Has a prescription dry body weight ≥40 kg. 14. Continues to meet inclusion criteria 1 through 7.

	15. Subjects do not have any safety or other reasons, which in the opinion of the Investigator, should exclude them from entering the open-label extension period.
Exclusion Criteria:	1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study. 2. Planned or anticipated to receive a kidney transplant during the study. Note: Being listed on a kidney transplant list is not an exclusion criterion. 3. Subjects with itching caused by conditions other than chronic renal failure or complications of chronic renal failure, which could affect the efficacy evaluation in the opinion of the Investigator (e.g., atopic dermatitis, chronic urticaria). Note: Subjects whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphataemia, anaemia, or the dialysis procedure, or prescription may be enrolled. 4. Has localised itch restricted to the palms of the hands. 5. Has pruritus only during the dialysis session (by subject report). 6. Subjects with severe hepatic impairment (Child-Pugh Class C) or concurrent hepatic cirrhosis. 7. Subject is receiving ongoing ultraviolet B treatment and anticipates receiving such treatment during the study. 8. Subjects who previously were enrolled in any clinical study of difelikefalin and received at least 1 dose of difelikefalin. 9. Significant systolic or diastolic heart failure (e.g., New York Heart Association Class IV congestive heart failure) (Appendix 2). 10. Subjects with concurrent malignancy except excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ that has been excised or resected completely. 11. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening. 12. Severe mental illness or cognitive impairment (e.g., dementia) or other concurrent mental disorder that, in the opinion of the Investigator, would compromise the validity of study measurements. 13. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (e.g., diagnosis of encephalopathy, coma, delirium). 14. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening. 15. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening. 16. Subject is receiving prohibited medication (e.g., nalfurafine hydrochloride, opioid antagonists)

	17. Subjects who received treatment with any investigational product or study device in a clinical study (including clinical studies of medical devices or cellular and tissue-based products) within 30 days prior to the informed consent procedure, or who are planning to participate in another clinical study before the end of the follow-up period of this study.
Primary and Secondary Endpoints:	**Efficacy Endpoints** Primary Endpoint • Change from baseline in the weekly mean of the daily 24-hour Worst Itching Intensity NRS (WI-NRS) score at Week 4 of the double-blind period.* *The degree of the most intense itching within a day will be assessed using NRS scores. Secondary Endpoints • Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period. • Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period. • Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period. • Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period. • Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period. • Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period. • Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score. • Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the Skindex-10 scale total score. • Change from baseline in the weekly mean of the 24-hour WI-NRS score at each week of the double-blind period. • Change from baseline in itch-related QoL at each time point of the double-blind period and open-label extension phase, as assessed by the 5-D itch scale total score. • Change from baseline in itch-related QoL at each time point of the double-blind period and open-label extension phase, as assessed by the Skindex-10 scale total score.

	• Patient Global Impression of Change. **Safety Endpoints** • Overall safety and tolerability of difelikefalin as assessed by incidence of AEs, 12-lead electrocardiogram (ECG), vital signs, and clinical safety laboratory evaluations over the study period.
Procedures:	**Double-Blind Period** The double-blind phase of the study will consist of a screening visit, a 7-day run-in period, and a 12-week double-blind period. Informed consent will be obtained prior to performing any study-specific procedures. See Table 1 for full details of protocol required assessments, procedures, and applicable visits (and timings of each visit) during the double-blind period. The screening visit will occur within 7 to 28 days prior to randomisation to assess eligibility. The site has also the option to conduct the screening visit within the run-in period at the discretion of the Investigator. Eligible subjects will complete a 7-day run-in period during the week prior to randomisation to confirm eligibility, preferably starting on the first dialysis session of that week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule). The purpose of the run-in period is to confirm that each subject has moderate-to-severe pruritus (i.e., weekly average WI-NRS ≥5), as measured by the subject-daily reported 24-hour WI-NRS, and to establish a baseline itch intensity. Subjects must not be informed that they need to report a weekly average worst itch score ≥5 to be enrolled in the study. During the first visit of the run-in period, subjects will be trained on completion of the 24-hour WI-NRS and will start the reporting of their WI-NRS daily score. For consistency, subjects will be requested to complete the NRS worksheets (either at home or in the dialysis unit, as required) each day at a similar time of day around the normal start time of their dialysis. Subjects will be trained on other itch-related patient reported outcome (PRO) worksheets during the run-in period or on Day 1 of the double-blind period at the latest. If subjects continue to meet all inclusion and no exclusion criteria at the end of the 7-day run-in period, they will be randomised on Day 1 into the double-blind period in a 1:1 ratio to receive either difelikefalin or placebo. Subjects will be stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to randomisation (run-in period) as well as the presence or absence of specific medical conditions. These specific medical conditions include: • History of fall or fracture (related to fall) • Confusional state or mental status change or altered mental status or disorientation • Gait disturbance or movement disorder

	Day 1 of the double-blind period will be defined as the day of administration of the first dose of investigational product and will occur preferably on the first dialysis session of the first treatment week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule). Subjects will be administered investigational product after the end of each dialysis session during the 12-week double-blind period. Each subject is to receive investigational product 3 times weekly for a total of 36 doses. Prescription dry body weight will be recorded during screening and on Day 1 of the double-blind period. During the double-blind period, subjects will continue to report their daily WI-NRS score over the previous 24 hours. In addition, during selected study visits (Day 1 and first day of Weeks 5, 9 and 13, i.e., Days 29, 57 and 85), they will complete other PRO measures (Skindex-10 scale and 5-D itch scale). The subjects will complete the Patient Global Impression of Change at the end of the double-blind phase (Day 85). Subjects will be instructed to record PRO measurements, including WI-NRS scores, at a similar time of day, whether in the dialysis unit (on dialysis days) or at home (on non-dialysis days). Blood samples for clinical laboratory tests will be collected at the screening visit and on Days 1 and 85; in addition, blood samples for analysis of serum potassium will be collected every 2 weeks (on dialysis days). 12-lead ECG will be monitored at the screening visit and on Day 85. Vital signs will be monitored periodically, and AEs, and concomitant medications will be continuously recorded during the double-blind phase. A structured safety evaluation will be performed once during the run-in period and weekly (preferably on Wednesday/Thursday) during the double-blind period. The structured safety evaluation is performed by study staff using a list of specific signs/symptoms (e.g., mental status change, gait disturbance). **Open-label Extension Period** Subjects who received at least 30 doses of investigational product (difelikefalin or placebo) during the 12-week double-blind period and continue to meet other eligibility criteria will be eligible to receive open-label difelikefalin for an additional 14 weeks. See Table 2 for full details of protocol required assessments, procedures, and applicable visits (and timings of each visit) during the open-label period. Each subject will receive difelikefalin at a dose of 0.5 µg/kg after the end of each dialysis session, 3 times per week for up to 14 weeks, regardless of whether they had been previously administered placebo or difelikefalin. Prescription dry body weight will be recorded at the start of the open-label extension phase; if there is a ±10% or more change from the prescription dry body weight recorded at screening, then the difelikefalin dose will be adjusted according to the newly recorded dry body weight.

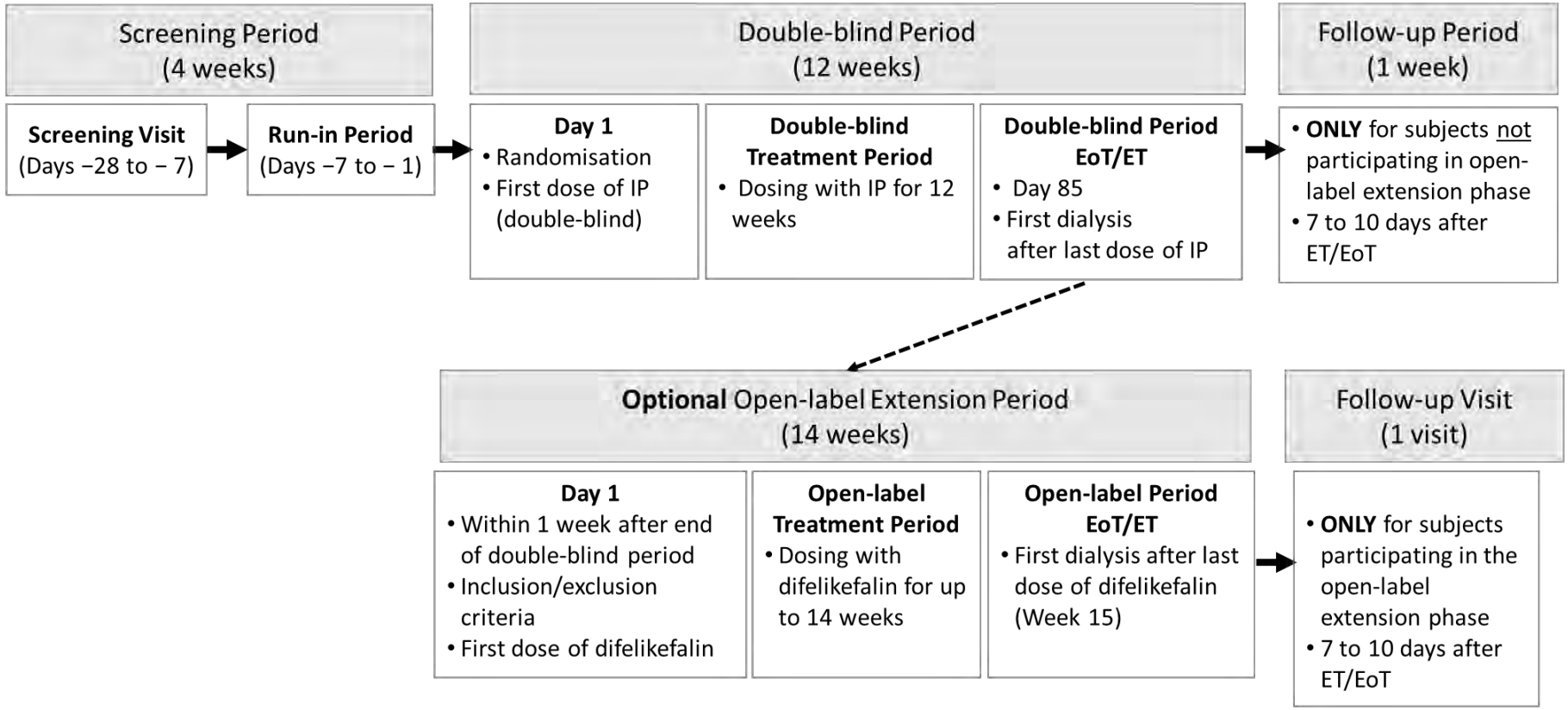
	The first visit and first dosing for the open-label extension phase of the study will occur immediately on the day of the last visit of the double-blind period or up to 1 week following the double-blind period. Day 1 of the open-label extension period will be defined as the day of administration of the first dose of difelikefalin in the open-label extension period and will occur preferably on the first dialysis session of the first treatment week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule). The last dose of open-label difelikefalin will be administered at the last dialysis visit on Week 14, or early termination. Subjects will complete the Skindex-10 scale and 5-D itch scale at Week 4, Week 8, Week 12 and at the end-of-treatment visit, which corresponds to the first dialysis visit following the last dose of difelikefalin given in the open-label extension (i.e., first dialysis on Week 15). Blood samples for clinical laboratory tests will be collected at the end of treatment or early termination visit; in addition, blood samples for analysis of serum potassium will be collected every 2 weeks (on dialysis days), i.e., at Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12 of the open-label extension. Vital signs will be monitored on Day 1, at Week 4, Week 8, Week 12 and at the end of treatment or early termination visit. AEs and concomitant medications will be continuously recorded throughout the open-label treatment period. 12-lead ECGs will be monitored at the open-label end of treatment or early termination visit. **Follow-up Period** A final safety follow-up visit will be conducted in 7 to 10 days: • After the end-of-treatment visit of the double-blind period for subjects not participating in the open-label extension phase • After the end-of-treatment visit of the open-label extension period for subjects participating in the open-label extension phase • Or after the early termination visit during either the double-blind period or the open-label extension phase
Sample Size:	**Double-blind Period** Based on the results observed at the end of Week 4 in a Japanese Phase 2 clinical study (MR13A9-4) and in the pooled data of 2 Phase 2 clinical studies (CLIN3102 and CLIN3103), a mean difference of −0.9 with a common standard deviation (SD) of 2.1 is assumed between difelikefalin and the placebo group regarding the primary endpoint. Assuming a 2-sided significance level of 5% and a statistical power of 90%, 116 subjects per group will be required to detect a difference of -0.9, with a common SD of 2.1, between the difelikefalin and the placebo group using a 2-sample t-test. In addition, assuming, a 10% drop out rate, 258 subjects in total need to be enrolled in the double-blind study period, i.e., 129 subjects per group. Please refer to Section 12.2 of the protocol for further details.

	Open-label Extension Period All subjects who completed the double-blind period may continue into the 14-week open-label extension period if they meet the eligibility criteria.
Study Sites:	30-40 study sites in China
Statistical Methods:	Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be finalised prior to database lock. Any deviation from the SAP will be noted and explained in the clinical study report. An interim analysis may be conducted. Details will be defined in the SAP. **Analysis Populations** The following subject populations will be used for presentation and analysis of the data: • The double-blind safety analysis set (DB-SAF) is defined as all randomised subjects who receive at least 1 dose of investigational product during the double-blind period. Subjects in the DB-SAF will be analysed according to the actual treatment received. The DB-SAF will be used to analyse exposure data as well as all safety endpoints collected during the double-blind period. • The full analysis set (FAS) is defined as all subjects who satisfy the following criteria: – Randomised to treatment – Received at least 1 dose of investigational product – Had a non-missing baseline assessment for the weekly mean of the daily 24-hour WI-NRS score – Had at least 1 post-baseline assessment for the weekly mean of the daily 24-hour WI-NRS score. Subjects in the FAS will be analysed according to their randomised treatment, regardless of the actual treatment received. The FAS will be used to analyse all efficacy endpoints collected during the double-blind period. • The per-protocol set (PPS) consists of all subjects who, in addition to the FAS criteria, do not have any major protocol deviations that will be defined and reviewed during the blinded data review meeting prior to unblinding the data. Subjects in the PPS will be analysed according to their randomised treatment, regardless of the actual treatment received. The PPS will be used to analyse efficacy endpoints collected during the double-blind period. • The open-label safety analysis set (OL-SAF) consists of all subjects who receive at least 1 dose of investigational product in the open-label extension period. Subjects in the OL-SAF will be analysed according to the actual treatment sequence received during the double-blind and open-label periods. The OL-SAF will be used to analyse exposure data to difelikefalin, efficacy as well as all safety endpoints collected during the open-label extension period.

	Frequency tables for categorical variables (absolutes and relative frequencies) and descriptive statistics for continuous variables (i.e., number of subjects, mean, SD, minimum, median, quartiles, and maximum) will be calculated and presented by treatment groups. Demographic and baseline disease characteristics will be summarised descriptively by treatment groups. Subject exposure and compliance will be calculated and summarised descriptively by treatment groups. **Primary Efficacy Endpoint Analyses (Double-blind Period)** The primary efficacy endpoint is defined as the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 (Days 23 to 29) of the double-blind period. The FAS will be used as the primary population for the analysis of the primary efficacy endpoint as well as for its sensitivity analysis. The PPS will be used as a secondary population. The weekly mean of the 24-hour WI-NRS score will be defined as the sum of the daily WI-NRS score reported during a specific week during the double-blind period (e.g., Days 2 to 8, Days 9 to 15, Days 16 to 22, Days 23 to 29) divided by the number of days with non-missing scores for that week. If the daily WI-NRS is missing for >3 days during a specific week, the corresponding weekly mean WI-NRS will be set to missing. The baseline score will be defined as the average of the daily 24-hour WI-NRS scores collected over the run-in period, including pre-randomisation assessments collected on Day 1. The change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 (Days 23 to 29) of the double-blind period will be analysed using a mixed-effect model for repeated measures (MMRM). Missing scores will not be imputed. Assuming that the data are missing at random (MAR), the estimates of the treatment differences calculated from the MMRM described below are unbiased. The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline NRS score, use of prior anti-itch medication and presence of specific medical conditions as covariates. Repeated measures will include values collected at the end of Weeks 1, 2, 3, and 4. An unstructured covariance matrix will be used to model the within-subject errors. Should the model fail to converge, a compound symmetric covariance matrix will be used instead. The Kenward-Roger2 approximation will be used to estimate the denominator degrees of freedom. Standard descriptive statistics will be reported on the values and changes from baseline at Week 4 of the double-blind period along with the adjusted mean change at Week 4 for each group and its 2-sided 95% confidence interval (CI). The adjusted mean treatment difference in the change between difelikefalin and placebo groups will be estimated at Week 4 of the double-blind period as the simple contrast in the treatment effect. Its 2-sided 95% CI as well as its p-value will be presented.

	Testing of the primary efficacy endpoint will be 2-sided and conducted at the 5% error level. The null hypothesis in this study is that there is no treatment difference in the primary efficacy analysis of the primary endpoint, i.e., the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period. The alternative hypothesis is that subjects randomised to difelikefalin experience significantly less itching compared to subjects randomised to placebo. In the primary efficacy analysis, missing NRS data will not be imputed. Sensitivity analyses of the primary efficacy endpoint using multiple imputed data will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms, as detailed in Section 12.8.1 of the protocol. **Secondary Efficacy Endpoints Analyses** Secondary and other efficacy endpoints will be analysed using the FAS, as the primary population, and PPS, as a secondary population. Significance level is set at an alpha of 0.05 (2-sided) and no adjustment will be made for testing multiple secondary outcomes. Some significant findings are expected to occur by chance so undue consideration will not be given to any particular significant difference. Moreover, interpretation of the results will be based on patterns of differences and in conjunction with the results of the primary analyses. Secondary efficacy endpoints will be analysed as per Section 12.8.2 of the protocol. **Safety Analyses** Safety data will be summarised descriptively for each study period. No inferential statistics are planned. Analyses of safety data will include summaries of AEs including adverse events of special interest (AESIs), serious adverse events (SAEs) and AEs resulting in study drug discontinuation. AEs will be tabulated by system organ class (SOC) and preferred term (PT), using Medical Dictionary for Regulatory Activities (MedDRA) coded terms. Incidence of AEs will also be summarised by maximum intensity and maximum relationship to the investigational product. Vital signs, biochemistry, and haematology data, and 12-lead ECG data will be descriptively summarised by visit as applicable, in addition to change from baseline for each study period.

Figure 1 Study Design



Notes: Conditionally permitted concomitant medications (anti-itch drugs) are allowed throughout the study.
EoT=End of treatment; ET=Early termination; IP=Investigational product.

Table 1 Schedule of Events and Assessments for the Double-blind Period

Study Procedures	Screening Period		Double-blind Period[2]						Double-blind End of Treatment[3]/ Early Termination	Follow-Up Period (ONLY for Subjects not Participating in Open-label Extension Phase)
	Screening Visit[1]	Run-in Period[1]								
Visit Days	**Day -28 to Day -7**	**Day -7 to Day -1**	**Week 1**			**Weeks 2 to 12**			**Week 13**	**Follow-up Day 1 to 10 after EoT**
			M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
	-28 to -7	**-7 to -1**	**1**	**3**	**5**				**85**	**85 to 95**
Administrative Procedures										
Informed consent	X									
Dispense subject identification card	X									
Inclusion/exclusion criteria	X		X[4]							
Medical history/prior medications (including antipruritic medications)/demographics	X	X[4]	X[4]							
Randomisation			X							
Safety and efficacy evaluations										
Physical examination	X									
Prescription dry body weight	X		X							
Pre-dialysis 12-lead ECG[5]	X[5]								X[5]	
Pre-dialysis vital signs	X		X[6]			X[6]			X[6]	X[7]
Haematology, serum chemistry (pre-dialysis)[8]	X		X						X	
Separate serum potassium						X[9]				
Serum pregnancy (females of childbearing potential only)	X[10]								X	
Subject training on PRO worksheets		X[11,12]	X[12]						X	
Worst Itching Intensity NRS (daily)[13]		X	Record on an ongoing basis						X	X[14]

Study Procedures	Screening Period		Double-blind Period[2]						Double-blind End of Treatment[3]/ Early Termination	Follow-Up Period (ONLY for Subjects not Participating in Open-label Extension Phase)
	Screening Visit[1]	Run-in Period[1]								
Visit Days	**Day -28 to Day -7**	**Day -7 to Day -1**	**Week 1**			**Weeks 2 to 12**			**Week 13**	**Follow-up Day 1 to 10 after EoT**
			M/Tu	**W/Th**	**F/Sa**	**M/Tu**	**W/Th**	**F/Sa**		
	-28 to -7	**-7 to -1**	**1**	**3**	**5**				**85**	**85 to 95**
5-D itch scale, Skindex-10 scale[15]			X			X[15]			X[15]	
Patient Global Impression of Change									X	
IV administration of investigational product			Record on an ongoing basis							
Adverse event monitoring	X	X	Record on an ongoing basis						X	X
Concomitant medications (including antipruritic medications)[16]			X	Record on an ongoing basis					X	X
Structured safety evaluation[17]		X		X			X			X

1 Sites have the option to conduct the screening visit during the run-in period at the discretion of the Investigator.
2 Each visit during the double-blind period will coincide with the subject's normal dialysis treatments.
3 The end-of-treatment visit in the double-blind phase will be the first dialysis visit following the last dose of investigational product (i.e., first dialysis on Week 13 (Day 85)), which also corresponds to Day 1 of the first day of the open-label extension. For subjects not participating in the open-label extension, Day 85 corresponds to Day 1 of the follow-up period.
4 Medical history will be updated on Day 1 with any changes since the screening visit, and inclusion/exclusion criteria will be confirmed prior to randomisation. Antipruritic medication will be updated at each dialysis visit during the run-in period.
5 12-lead ECG must be performed prior to the start of dialysis at screening, Day 85 (double-blind period end of treatment), or at early termination visit.
6 Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, will be recorded on Days 1, 15, 29, 43, 57, 71 and 85 (double-blind period end of treatment), or at early termination visit only when the subject is in a sitting or semi-recumbent position. Heart rate will be measured at each dialysis; if heart rate is clinically significant at visits outside the pre-specified visits per Schedule of Events, the heart rate will be recorded in the eCRF.
7 Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, will be recorded at the follow-up visit (at 7 to 10 days after EoT/ET visit). Heart rate will be measured at each dialysis visit during the follow-up period; if heart rate is clinically significant at visits outside the follow-up visit, the heart rate will be recorded in the eCRF.
8 Blood samples for clinical laboratory evaluation will be taken at screening, and on Days 1 and 85 (double-blind period end of treatment), or at early termination visit only and will be assessed at central laboratory. Haematology will include basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, haemoglobin, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, red blood cells, white blood cells. Serum chemistry will include albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin (total), BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium.
9 Serum potassium will be assessed separately at Weeks 3, 5, 7, 9 and 11 (Days 15, 29, 43, 57 and 71) (central laboratory assessment).
10 Within 7 days prior to first dose of investigational product (central laboratory assessment).
11 Training on Worst Itching Intensity NRS will be conducted on the first day of the run-in period (Day -7).

12 Training on Skindex-10 scale and 5-D itch scale may be performed at any time during the week prior to randomisation or on Day 1 of the double-blind period.
13 Subjects will be requested to complete their Worst Itching Intensity NRS worksheets each day at a similar time (either at home on non-dialysis days around the normal start time of their dialysis or in the dialysis unit). On dialysis days, the worksheets will be completed prior to or during dialysis, but must be completed prior to dosing.
14 During the follow-up period, Worst Itching Intensity NRS worksheets will be completed on dialysis days only.
15 5-D itch scale and Skindex-10 scale will be completed on Day 1 and the first visit of Week 5 (Day 29), Week 9 (Day 57) and Week 13 (Day 85). 5-D itch scale will preferably be completed first. If the first visit of the week is missed, the subject may complete the worksheets at their next visit for the same week. The worksheets will be completed prior to or during dialysis (preferably within 1 hour of the dialysis) but must be completed prior to dosing.
16 Concomitant medications including antipruritic medication will be updated at each dialysis visit during the double-blind period, and until the end of the follow-up period.
17 A list of specific signs/symptoms will be verified with the subject by qualified site staff, preferably to be completed on Wednesday/Thursday each week during the run-in period, the double-blind period, and the discontinuation period. Not to be completed on Monday/Tuesday (see Section 10.8.4.1 for a list of the AESIs).

Notes: AESI=Adverse event of special interest; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BUN=Blood urea nitrogen; ECG=Electrocardiogram; eCRF=Electronic Case Report Form; EoT=End of treatment; F=Friday; IV=Intravenous; M=Monday; MCH=Mean corpuscular haemoglobin; MCHC=Mean corpuscular haemoglobin concentration; MCV=Mean corpuscular volume; NRS=Numerical Rating Scale; PRO=Patient reported outcome; RDW=Red blood cell distribution width; S=Saturday; SGOT=Serum glutamic-oxaloacetic transaminase; SGPT=Serum glutamic-pyruvic transaminase, Th=Thursday; Tu=Tuesday; W=Wednesday.

Table 2 Schedule of Events and Assessments for the Open-label Extension Period

Study Procedures	Open-label Treatment Period[1]							EoT/ Early Termination	Follow-Up
	Day 1[2]	Week 2[1]	Week 4[1]	Week 6[1]	Week 8[1]	Week 10[1]	Week 12[1]	First Dialysis of Week 15[3]	7 to 10 Days After EoT/ Early Termination[4]
Inclusion/exclusion criteria	X[5]								
Physical examination	X								
Prescription dry body weight[6]	X						X		
Pre-dialysis 12-lead electrocardiogram[7]								X	
Pre-dialysis vital signs[8]	X		X		X		X	X	X
Haematology, serum chemistry (pre-dialysis)								X	
Serum potassium (pre-dialysis)		X	X	X	X	X	X		
Serum pregnancy test for women of childbearing potential only								X	
5-D itch scale, Skindex-10 scale[9]			X		X		X	X	
IV administration of investigational product	After each dialysis, up to Week 14 included								
Adverse event monitoring	Record on an ongoing basis[10]								
Concomitant medications (including antipruritic medications)	Record on an ongoing basis[10]								

1 Each visit during the open-label treatment period will coincide with the subject's normal dialysis treatments. The study visit may occur on any chosen dialysis day of a scheduled week if all assessments are completed during that visit.
2 Day 1 of the open-label treatment period corresponds to the day of the last visit of the double-blind period or up to 1 week following the double-blind period.
3 The end-of-treatment visit will be the first dialysis visit following the last dose of investigational product (i.e., first dialysis on Week 15).
4 The follow-up visit will coincide with a dialysis day.
5 Prior to dosing on Day 1 of the open-label treatment period, the inclusion/exclusion criteria will be confirmed.
6 The prescription dry body weight will be captured from the dialysis prescription and will be recorded on Day 1 and at Week 12. If there is a >10% change in prescription dry body weight compared to the last value, then the difelikefalin dose will be adjusted.
7 Electrocardiogram must be performed prior to the start of dialysis.

8 Vital signs, including body temperature, heart rate, and blood pressure, will be obtained at the specified visits while the subject is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate will be measured at each dialysis; if the heart rate is clinically significant at visits outside the pre-specified visits per Schedule of Events, the heart rate will be recorded in the eCRF.
9 To be completed before or during dialysis (preferably within 1 hour of the dialysis but before dosing). 5-D itch scale will preferably be completed first.
10 Adverse events and concomitant medications will be recorded starting on Day 1 of the open-label treatment period.
Notes: eCRF=Electronic Case Report Form; EoT=End of treatment; IV=Intravenous.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CI	confidence interval
CKD	chronic kidney disease
CKD-aP	chronic kidney disease-associated pruritus
C_{max}	maximum concentration
CNS	central nervous system
CRO	Contract Research Organisation
DB-SAF	double-blind safety analysis set
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	electronic data capture
ESRD	end-stage renal disease
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
Hb	haemoglobin
HD	haemodialysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IV	intravenous
KOR	kappa opioid receptor
LS	least squares

MAR	missing at random
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
NRS	Numerical Rating Scale
OL-SAF	open-label safety analysis set
PK	pharmacokinetic
PPS	per-protocol set
PRO	patient reported outcome
PT	preferred term
QoL	quality of life
RBCs	red blood cells
RDW	red blood cell distribution width
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
US	United States
WBCs	white blood cells
WI-NRS	Worst Itching Intensity Numerical Rating Scale

1. INTRODUCTION AND BACKGROUND

Difelikefalin is a novel, selective KOR agonist that is being developed as a therapeutic agent for the symptomatic relief of pruritus and pain.

Chronic kidney disease-associated pruritus (CKD-aP), also known as uraemic pruritus, is a distressful medical condition, common in >60% of CKD patients undergoing HD [1]. However, there are currently no approved treatments for CKD-aP in China. Difelikefalin is a KOR agonist with limited central nervous system (CNS) penetration that aims to fill this void by effectively and safely reducing itch in HD patients. Difelikefalin has been approved for marketing in the US on 23 August 2021 and it is expected to be approved in the EU in May 2022.

1.1 Background of the Disease and Treatment Options

CKD-aP is characterised by a generalised and persisting itch, which has a negative impact on QoL and is associated with depression, anxiety, sleep disturbance, and increased mortality. The incidence of CKD-aP is decreasing given advances in HD technology; however, approximately 42%, 21%, 11%, and 8% of HD patients in China, are somewhat bothered, moderately bothered, very much bothered, or extremely bothered by pruritus [1]. In a single-centre study in China described by Li et al, 2015, the prevalence of uraemic pruritus was reported to be 65.2% in continuous ambulatory peritoneal dialysis patients [2]. In another single-centre study conducted in China, Wen et al, 2020 reported that over 80% of HD patients were bothered by uraemic pruritus (among those bothered, 36-57% had moderate-to-severe pruritus) [3].

The pathophysiology of CKD-aP is not well understood; however, it is multifactorial and is attributed to imbalance of opioid receptors, uraemic toxins build-up, immune system dysregulation, systemic inflammation, peripheral neuropathy, hyperparathyroidism, etc [4,5].

Treatment of pruritus in HD patients depends on the severity of itching; treatment varies from use of topical therapy (emollients, steroid analgesics, local anaesthetics) in patients with mild or localised symptoms, to optimisation of dialysis parameters and systemic treatment in patients with more severe or generalised itching [6]. However, many patients have an inadequate response to existing treatments (topical or internal). Nalfurafine hydrochloride, an oral mixed nonselective mu partial agonist/KOR agonist is effective in treating pruritus; however, because of the oral formulation, HD patients have to take a large number of tablets, which increases the already high burden of these patients having to take many oral drugs. In addition, many HD patients have decreased salivary secretion and restricted fluid intake, and thus may have difficulty in taking the oral drug. Furthermore, as nalfurafine hydrochloride activates KOR in the CNS and in the gastrointestinal tract, this frequently induces adverse drug reactions (ADRs), such as sleep loss and constipation [7]. This creates the need to develop new treatments that are more convenient for use and cause fewer ADRs.

Opioid receptors are involved in the modulation of pain and itching signals and are subdivided into 3 subtypes, classified as mu, kappa, and delta. These receptor subtypes are found in the CNS (i.e., brain and spinal cord), on sensory ganglionic neurons and their nerve fibres innervating peripheral tissues such as skin, and on certain cell types of the immune system. The mu opioid receptor binds to β-endorphin, inhibits pain and induces itching; KOR binds to dynorphin and inhibits pain and itching [8,9]. Morphine, the most widely clinically used opiate analgesic, acts primarily via activation of mu opioid receptors located in the CNS and peripheral nervous system. As such, it is associated with a wide array of side effects such as sedation, respiratory depression, abuse liability, constipation, cardiovascular collapse, and death. To avoid these undesirable effects, difelikefalin, a small, synthetic peptide KOR agonist, was designed. Difelikefalin has a limited entry into the CNS, thereby predominantly activating KORs expressed on peripheral neurons and immune cells.

Difelikefalin has greater than 30,000-fold selectivity over human mu and delta opioid receptors, and no significant detectable activity at other receptors, ion channels, transporters, or enzymes. The selective activity of difelikefalin at KORs avoids the mu opioid receptor associated side effects characteristic of most opioid analgesics, such as respiratory depression, dependence, and euphoria [10,11].

Because of its physicochemical properties (i.e., hydrophilic) difelikefalin is expected to be safer and more tolerable; difelikefalin does not pass through the blood-brain barrier, which limits such undesirable CNS effects as activation of central KORs, i.e., dysphoria and psychomimetic effects [10]. In addition, difelikefalin is mostly renally excreted, resulting in a long half-life in HD patients ($t_{½}$ about 24 hours) and clearance by dialysis (see the latest difelikefalin Investigator's Brochure (IB)).

Furthermore, difelikefalin is expected to enhance the quality of pharmaceutical management that includes treatment compliance, treatment instructions, and remaining drug check because it is an injectable formulation administered directly from the dialysis circuit at the end of each dialysis session without fail under the supervision of a physician.

1.2 Summary of Nonclinical and Clinical Data

1.2.1 Summary of Nonclinical Data

Provided here is a summary of the nonclinical data for difelikefalin. For more details, please refer to the latest version of difelikefalin IB.

- The physicochemical properties of difelikefalin (hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) minimise passive diffusion or active transport through the blood-brain barrier, thus limiting penetration into the brain. The limited to no brain exposure is further supported by radiolabelled studies and pharmacological studies suggesting that difelikefalin does not readily enter the CNS, and preferentially activates KORs located primarily in the peripheral nervous system and on immune cells.

- Nonclinical pharmacological studies indicate that difelikefalin has combined antipruritic, analgesic, and anti-inflammatory properties.

- Difelikefalin is primarily excreted unchanged into the urine and bile with no major metabolites identified. Nonclinical data indicate that difelikefalin should not significantly affect the clearance and/or metabolism of any co-administered drug(s).

- Generally, dose-proportional, linear pharmacokinetics (PK) in systemic exposure were observed following single IV or oral doses, with $t_{½}$ ranging from 1.1-5.5 hours. Similar kinetics were observed after repeated administration.

- No notable safety concerns after IV or oral administration of difelikefalin were identified in studies of acute and chronic toxicology (up to 6 months in the rat and 9 months in the monkey), safety pharmacology, reproductive and development toxicology, genotoxicity, and carcinogenicity.

1.2.2 Summary of Clinical Data

This will be the first Phase 3 clinical trial of difelikefalin in HD Chinese subjects with moderate-to-severe pruritus. However, PK, safety, and efficacy of IV difelikefalin for the treatment of CKD-aP in HD patients have been previously investigated in multiple Phase 1, 2, and 3 clinical studies conducted outside of China (including 2 Phase 1 and 2 Phase 2 clinical studies in Japan).

Difelikefalin has been evaluated as either IV bolus or 15-minute infusion as single or repeated doses ranging from 0.25 to 40 μg/kg. In the clinical development program, IV difelikefalin has been administered to 4,037 subjects; 2,672 subjects have received IV formulation, and 1,365 have received oral formulation. A total of 1,592 CKD subjects on HD have received IV difelikefalin; of these, 1,096 subjects have received IV difelikefalin for at least 12 weeks; and 415 subjects with moderate-to-severe pruritus have received IV difelikefalin for at least 48 weeks.

Considering all the data relevant to the efficacy and safety of IV difelikefalin, the benefit/risk profile of the product in patients with CKD-aP is considered favourable.

Provided below is a summary of the clinical data for difelikefalin. For more details, please refer to the latest version of difelikefalin IB.

1.2.2.1 Pharmacokinetics

In subjects with normal renal function, difelikefalin has linear and dose-proportional PK, with $t_{½}$ of approximately 2-3 hours after single-dose IV administration. In subjects with CKD on HD, $t_{½}$ increases at least 10-fold compared with subjects with normal renal function.

Following single-dose IV administration of (^{14}C)-difelikefalin to healthy volunteers or subjects on HD, >99% of circulating plasma radioactivity remained as unchanged difelikefalin.

In both healthy volunteers and subjects on HD, most of the dose excreted into urine and faeces was unchanged difelikefalin with minor quantities of putative metabolites, none exceeding 2.5%.

In a Japanese clinical pharmacology study in healthy subjects (Study PR-13A9-P1-A), the cumulative urinary excretion rate became almost constant by 36 hours after the initial dose (i.e., 15 hours after the final dose). The cumulative urinary excretion rate for up to 72 hours after the initial dose (i.e., 51 hours after the final dose) ranged from 71.6% to 76.8%, being similar across the dose groups (1.0, 3.0, 5.0, 10, 20, and 40 µg/kg).

In Japanese HD subjects (Study PR-13A9-P1-B), plasma difelikefalin concentrations after the first and third IV doses showed a biphasic elimination pattern of a rapid initial phase and a slow elimination phase. The $t_{½}$ of difelikefalin was 34.1 to 39.0 hours after the first dose and 40.0 to 49.3 hours after the third dose. The accumulation ratio of Day 5 to Day 1 calculated using the C_{max}, AUC_{0-48}, and trough values indicated a low likelihood of accumulation of difelikefalin.

1.2.2.2 Safety of IV Difelikefalin

In general, IV difelikefalin has been well tolerated in both single and repeat-dose clinical studies for up to 12 weeks at doses <5 µg/kg in healthy volunteers and subjects with CKD.

In subjects with normal renal function, IV difelikefalin produces a transient and generally dose-related increase in urine output without loss of electrolytes (0 to 12 hours after dosing). This aquaretic effect (i.e., free water loss) is a known pharmacological effect of KOR agonists and is managed with fluid replacement, as applicable.

In healthy volunteers exposed to IV difelikefalin, the most common treatment-emergent adverse events (TEAEs) (≥5.0% of subjects) with an incidence ≥1.0% greater compared with placebo were, in descending frequency, paraesthesia, hypoaesthesia, dizziness, sedation, headache, and fatigue. There was an apparent dose-response relationship with difelikefalin for the majority of TEAEs, with the highest incidence observed at IV difelikefalin doses >5 µg/kg. There was 1 reported SAE of sinus tachycardia in a difelikefalin-treated subject and none in placebo-treated subjects. No specific TEAEs leading to investigational product discontinuation occurred in >1 subject.

In subjects with CKD on HD exposed to IV difelikefalin, the most common TEAEs (≥5.0% of subjects) with an incidence ≥1.0% greater compared with placebo were, in descending frequency, diarrhoea, nausea, insomnia, fall, hypotension, abdominal pain, dizziness, vomiting, hyperkalaemia, headache, pneumonia, and dyspnoea. The most common SAEs (≥1.0% of subjects) among difelikefalin-treated subjects with an incidence ≥1.0% greater compared with placebo were, in descending frequency, pneumonia, fluid overload, sepsis,

hyperkalaemia, respiratory failure, mental status changes, acute myocardial infarction, gastrointestinal haemorrhage, syncope, asthenia, and non-cardiac chest pain. Observed SAEs were consistent with underlying medical conditions in the subject population. The most common TEAEs leading to investigational product discontinuation among difelikefalin-treated subjects were cardiac arrest, somnolence, and dizziness.

In a Japanese Phase 1 clinical study (Study PR-13A9-P1-A, healthy volunteers), blood sodium increased was reported in 4/6 subjects in the 5.0 µg/kg group during the repeated-dose period. These events were reported only in clinical studies in subjects with normal renal function and have not been reported in clinical studies in HD subjects.

In a Japanese Phase 2 clinical study (Study MR13A9-3, JapicCTI-163265, n=84 CKD-aP subjects on HD receiving difelikefalin), common TEAEs (reported in ≥10% of subjects) included blood thyroid stimulating hormone decreased, dizziness, blood prolactin increased, nausea, feeling abnormal, and somnolence. Study treatment was discontinued or interrupted due to 1 event in 1 subject in the 0.25 µg/kg group, 2 events in 2 subjects in the 0.5 µg/kg group, 1 event in 1 subject in the 1.0 µg/kg group, and 17 events in 10 subjects in the 1.5 µg/kg group. Dependency was assessed as being present in 2 subjects in the placebo group and 1 subject in the 0.5 µg/kg difelikefalin group.

In a Japanese Phase 2 clinical study (Study MR13A9-4, NCT03802617, n=184 CKD-aP subjects on HD receiving difelikefalin), common TEAEs (reported in ≥3% of subjects) included somnolence, dizziness, palpitations, vomiting, nausea, and blood thyroid stimulating hormone decreased. Study treatment was discontinued or interrupted due to 5 events in 4/61 subjects in the 0.5 µg/kg group and 6 events in 5/62 subjects in the 1.0 µg/kg group. Dependency was assessed as being absent in all evaluable subjects.

1.2.2.3 Efficacy of IV Difelikefalin

The efficacy of IV difelikefalin in reducing itch-related QoL in subjects with CKD on HD has been demonstrated in Phase 2 and Phase 3 clinical studies.

- In a Phase 2 study (CR845-CLIN2101) [12], the efficacy outcomes were similar across the 0.5, 1, and 1.5 µg/kg dose groups after each HD (i.e., 3 times a week; 8 weeks of treatment); with statistically significant differences favouring difelikefalin over placebo most often observed in the 0.5 µg/kg dose group. Together with the more favourable safety profile seen in the 0.5 µg/kg group, the 0.5 µg/kg dose group was selected for evaluation in Phase 3 studies (12 weeks of treatment).

- In a Japanese Phase 2 clinical study (MR13A9-3), 105 CKD-aP subjects on HD received IV difelikefalin (0.25, 0.5, 1.0, or 1.5 µg/kg), or placebo 3 times weekly for 2 weeks. The primary endpoint of change in visual analogue scale (i.e., change based on the larger visual analogue scale value either in the morning or the evening during the 7 days, the latter half of the treatment period) suggested a dose-dependent improvement by treatment with difelikefalin at doses ≥0.5 µg/kg.

- In a Japanese Phase 2 clinical study (MR13A9-4), 247 CKD-aP subjects on HD received IV difelikefalin (0.25, 0.5, or 1.0 µg/kg, or placebo 3 times weekly for 8 weeks). The primary variable of change from baseline in the mean NRS score at Week 8 of the treatment period (adjusted mean ± standard error) was −2.97±0.29 in the difelikefalin 0.25 µg/kg group, −3.65±0.30 in the 0.5 µg/kg group, and −3.64±0.30 in the 1.0 µg/kg group, compared with −2.86±0.29 in the placebo group. These results showed significant improvement in the difelikefalin 0.5 and 1.0 µg/kg groups compared with the placebo group, indicating a dose-response relationship showing a constant effect at doses of ≥0.5 µg/kg.

- In the first Phase 3 double-blind, randomised, placebo-controlled, parallel group US study (CR845-CLIN3102) [13] in subjects with CKD on HD with moderate-to-severe pruritus, IV bolus administration of difelikefalin 0.5 µg/kg after each HD (i.e., 3 times a week) for 12 weeks resulted in a significant effect, with a higher proportion of subjects treated with difelikefalin showing ≥3-point (least squares (LS) mean of 51.0% of difelikefalin subjects versus 27.6% of placebo subjects, $p<0.001$) and ≥4-point (LS mean of 38.9% of difelikefalin subjects versus 18.0% of placebo subjects, $p<0.001$) reductions in WI-NRS score at Week 12; the reduction in the severity of itch intensity was observed within 1 week of treatment. Significant improvements in itch-related QoL were observed in this study.

- In the second Phase 3 double-blind, randomised, placebo-controlled, parallel group global study (CR845-CLIN3103) in subjects with CKD on HD with moderate-to-severe pruritus, IV bolus administration of difelikefalin 0.5 µg/kg after each HD (i.e., 3 times a week) for 12 weeks resulted in a significant effect, with a higher proportion of subjects treated with difelikefalin showing ≥3-point (LS mean of 54.0% of difelikefalin subjects versus 42.2% of placebo subjects, $p=0.020$) and ≥4-point (LS mean of 41.2% of difelikefalin subjects versus 28.4% of placebo subjects, $p=0.010$) reductions in WI-NRS score at Week 12; the reduction in the severity of itch intensity was observed within 2 weeks of treatment. Improvements in itch-related QoL were also observed in this global study.

- In a Phase 3, 12-week, open-label study (CR845-CLIN3105) in subjects with CKD on HD with moderate-to-severe pruritus, difelikefalin 0.5 µg/kg IV resulted in a reduction in pruritus, as measured by the percentage of subjects with a ≥3-point (73.7%) and ≥4-point (59.3%) improvement in WI-NRS score. Improvements in itch-related QoL were also observed.

2. RATIONALE

2.1 Patient Need

The number of patients in China undergoing HD is increasing each year [14]. Approximately 42% of HD patients in China, are distressed by moderate or severe pruritus [1]. The benefits of the KOR agonist difelikefalin in reducing itch in CKD-aP patients undergoing HD has been demonstrated in multiple Phase 2 and Phase 3 clinical studies outside of China. Currently, in China, there are no approved KOR agonists for the treatment of itch in HD subjects with CKD-aP. Study KOR-CHINA-301 will be the first clinical trial of IV difelikefalin for the treatment of subjects with CKD-aP on HD to be conducted in China.

Clinical data outside of China have shown the benefits of difelikefalin in CKD-aP patients undergoing HD; IV difelikefalin was well tolerated with an acceptable safety profile in CKD-aP patients undergoing HD.

Considering all the data relevant to the efficacy and safety of IV difelikefalin, the benefit/risk profile of the product in subjects with CKD-aP is considered favourable. Treatment with difelikefalin is also expected to relieve pruritus in HD patients in the present study.

2.2 Study Design

This study is designed to evaluate efficacy and safety of 0.5 µg/kg IV difelikefalin in Chinese subjects with CKD on HD (3 times weekly) and with moderate-to-severe associated pruritus. A dialysis frequency of 3 times a week (versus twice weekly), is prevalent for the dialysis practice in China [14].

IV administration of difelikefalin will occur at the end of HD by using the return HD line or via injection directly into a vein.

This study design (dose, investigational product administration, duration of treatment) is based on Phase 2 and Phase 3 clinical trials with difelikefalin in subjects with CKD-aP on HD conducted by Cara Therapeutics, Inc. previously outside of China (including clinical trials conducted in Japan by licensees of Cara Therapeutics, Inc.).

This study consists of a double-blind, randomised, placebo-controlled, parallel group treatment period, and an optional open-label extension period.

During the double-blind period, subjects will be administered investigational product (difelikefalin or placebo) at the end of each dialysis session for 12 weeks (3 times weekly, 36 times in total). The duration of the double-blind period is enough for the evaluation of the efficacy and safety in comparison with placebo. In a Phase 2 study in Japan (MR13A9-4), the difference between difelikefalin (0.5 µg/kg) and placebo in reducing NRS score increased until Week 3 and remained about constant at later time points (until Week 8). Based on these results, in an ongoing Phase 3 study in Japan, the primary efficacy

endpoint will be evaluated at Week 4; the same approach is used in this study. Twelve-week double-blind treatment is also considered enough for the assessment of difelikefalin safety in comparison with placebo, as adverse reactions occur early during difelikefalin treatment.

At the end of the double-blind period, subjects will have the option to enter an open-label extension period, during which, difelikefalin will be administered at the end of each dialysis session for 14 weeks (3 times weekly, 42 times in total). Thus, all subjects completing the double-blind period will be given the chance to receive the active treatment during the open-label phase. The inclusion of 14 weeks open-label treatment will increase the total duration of exposure to 26 weeks (for subjects receiving difelikefalin during the double-blind and open-label phases) and will also increase the safety population, allowing for collection of more safety data. After last administration of investigational product (end of double-blind period or end of open-label extension period or early discontinuation), subjects will enter a 1-week follow-up period (1 week to 10 days).

This study design (dose, investigational product administration, duration of treatment) is based on Phase 2 and Phase 3 clinical trials with difelikefalin in subjects with CKD-aP on HD conducted by Cara Therapeutics, Inc. previously outside of China (including clinical trials conducted in Japan by licensees of Cara Therapeutics, Inc.).

2.3 Dose Selection

The dose to be evaluated in this study, a single dose of 0.5 µg/kg difelikefalin (administered 3 times weekly), is based on clinical studies conducted outside of China. The dose of 0.5 µg/kg IV difelikefalin was shown to be effective and with a favourable safety profile in global studies and in clinical studies in Japan. A lower dose (0.25 µg/kg) did not show efficacy in a Phase 2 study in Japan (M13A9-4); a higher dose (1 µg/kg) was shown to be effective in Western subjects and in Japanese subjects; however, the incidence of AEs also increased in a dose-dependent manner.

The efficacy of 0.5 µg/kg IV difelikefalin in reducing itch in HD subjects with CKD-aP has been confirmed in 2 pivotal, Phase 3, randomised 12-week placebo-controlled studies, demonstrating statistically significant and clinically relevant reductions in pruritus. The treatment effect started as early as 1 week after initiating treatment, and the benefit was maintained for at least 1 year in the long-term extensions of these studies. No unexpected safety signals emerged during long-term treatment of up to 52 weeks with 0.5 µg/kg IV difelikefalin, with the nature and rate of the reported safety events aligning with published morbidity and mortality data of patients with CKD-aP undergoing HD.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To evaluate the efficacy of difelikefalin 0.5 μg/kg compared to placebo in reducing the intensity of itch in HD Chinese subjects with moderate-to-severe pruritus.

3.2 Secondary Objectives

- To evaluate the efficacy of difelikefalin 0.5 μg/kg compared to placebo in improving the itch-related QoL in HD Chinese subjects with moderate-to-severe pruritus.

- To evaluate the safety of difelikefalin 0.5 μg/kg in HD Chinese subjects with moderate-to-severe pruritus.

3.3 Primary Efficacy Endpoint

- Change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period*.

*The degree of the most intense itching within a day will be assessed using NRS scores.

3.4 Secondary Efficacy Endpoints

- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.

- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.

- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.

- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.

- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.

- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.

- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score.

- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the Skindex-10 scale total score.

- Change from baseline in the weekly mean of the 24-hour WI-NRS score at each week of the double-blind period.

- Change from baseline in itch-related QoL at each time point of the double-blind period and open-label extension phase, as assessed by the 5-D itch scale total score.

- Change from baseline in itch-related QoL at each time point of the double-blind period and open-label extension phase, as assessed by the Skindex-10 scale total score.

- Patient Global Impression of Change.

3.5 Safety Endpoints

Overall safety and tolerability of difelikefalin as assessed by incidence of AEs, 12-lead ECG vital signs, and clinical safety laboratory evaluations over the study period.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 3, multicentre, controlled, randomised study to evaluate the efficacy and safety of difelikefalin 0.5 µg/kg compared to placebo in reducing the intensity of itch in adult Chinese HD subjects with moderate-to-severe pruritus (Figure 1).

The study includes a 12-week double-blind placebo-controlled treatment period and a 14-week optional open-label extension period. A 4-week period (including a 7-day run-in period during the week prior to randomisation) before entry into the double-blind period is defined as the screening period, during which subjects will receive no investigational product.

Subjects eligible for randomisation in the double-blind part of the study will be randomised 1:1 to either difelikefalin or placebo treatment groups and will receive a randomisation number. Subjects will be stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to randomisation (run-in period) as well as the presence or absence of specific medical conditions. These specific medical conditions include:

- History of fall or fracture (related to fall)
- Confusional state or mental status change or altered mental status or disorientation
- Gait disturbance or movement disorder

Randomised subjects who terminate their study participation for any reason regardless of whether the investigational product was administered or not, will retain their randomisation number. The next subject will be given the next randomisation number.

During the double-blind period, the investigational product will be injected into the venous line of the dialysis circuit at the end of each dialysis session for 12 weeks (3 times weekly, 36 times in total). The dose of the investigational product will be determined based on the subject's prescription dry body weight (i.e., the target post-dialysis weight, as determined by the patient's nephrologist or dialysis unit) at the start day of the double-blind treatment period. The first dose of investigational product will be administered on Day 1, which will occur preferably on the first dialysis session of the first treatment week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule).

During the open-label extension period, difelikefalin will be administered for 14 weeks (3 times weekly), starting at Week 13, and will be given until Week 26 inclusive. The first visit and first dosing for the open-label extension phase of the study will occur immediately on the day of the last visit of the double-blind period or up to 1 week after the end of the double-blind period. The participation in the open-label extension period is optional.

The study also includes a 1-week (1 week to 10 days) follow-up period after last administration of investigational product (end of double-blind period or end of open-label extension period or early discontinuation).

Throughout the study, subjects will continuously use any conditionally permitted concomitant medications (e.g., to treat symptoms of chronic renal failure or other comorbidities) used at the start of the screening period. Please refer to Section 6.8 for details on concomitant treatments and therapies.

The schedule of assessments is provided in Table 1.

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is 31 to 32 weeks: screening period duration is 4 weeks (including a 7-day run-in period); treatment period duration is 12 weeks; open-label extension period (optional) is 14 weeks (starting within 1 week after the end of double-blind period), and follow-up period is 1 week (1 week to 10 days). For subjects not participating in the open-label extension period, the total study duration is 17 weeks.

The end of study is defined as the last subject last visit.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

5.1.1 Double-blind Period

Based on the results observed at the end of Week 4 in a Japanese Phase 2 clinical study (MR13A9-4) and in the pooled data of 2 Phase 3 clinical studies (CLIN3102 and CLIN3103), a mean difference of −0.9 with a common SD of 2.1 is assumed between difelikefalin and placebo group regarding the primary endpoint. Assuming a 2-sided significance level of 5% and a statistical power of 90%, 116 subjects per group will be required to detect a difference of -0.9, with a common SD of 2.1, between the difelikefalin and the placebo group using a 2-sample t-test. In addition, assuming a 10% drop out rate, 258 subjects in total need to be enrolled in the double-blind study period, i.e., 129 subjects per group.

5.1.2 Open-label Extension Period

All subjects who completed the double-blind period may continue into the 14-week open-label extension period provided they meet the eligibility criteria on Day 1 of the open-label extension period.

5.2 Inclusion Criteria

Double-blind Period

The double-blind period of this study will enrol HD subjects with pruritus who meet all the inclusion criteria and none of the exclusion criteria listed below.

1. Subject (or legally accepted representative) has provided written informed consent. Written informed consent must be provided before any study-specific procedures are performed including screening procedures.

2. Chinese subjects aged ≥18 to 85 years (inclusive) at the time of consent.

3. Able to communicate clearly with the Investigator and staff, able to understand the study procedures, and able and willing to comply with the study requirements, including providing written responses to questionnaires.

4. Subjects with CKD on HD 3 times weekly for ≥12 weeks prior to the informed consent procedure (including the date of informed consent) who can continue HD without changing its frequency or method.

   Note 1: Any temporary change in dialysis frequency or method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable, from the date of informed consent until the end of the follow-up period. Subjects routinely on 4 dialyses a week will not be eligible.

Note 2: Subjects receiving in-home HD may participate as long as they have switched to in-centre HD at least 2 weeks prior to screening and plan to remain on in-centre HD for the duration of the study.

Note 3: Subjects receiving alternate dialysis modalities such as nocturnal dialysis will not be eligible.

5. If female, is not pregnant, or nursing.

6. If female:

   a. Is surgically sterile; or

   b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or

   c. Has a negative serum pregnancy test within 7 days before first dose of investigational product and agrees to use acceptable contraceptive measures (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after the last dose of investigational product. Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed.

7. If male, agrees not to donate sperm after the first dose of investigational product administration until 7 days after the last dose of investigational product, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of investigational product. Note: No restrictions are required for a vasectomised male, provided his vasectomy was performed ≥4 months prior to screening.

8. Subjects whose NRS score (Appendix 1) in the 7-days run-in period (7 days including the score recorded on the start day of treatment) meets both of the below:

   a. NRS scores have been recorded for at least 4 days through a 7-day run-in period.

   b. The mean value of the recorded scores is ≥5.0 (moderate-to-severe pruritus).

9. Subjects with a prescription dry body weight between 40 and 100 kg, inclusive.

10. Over the last 3 months prior to screening, has had at least 1 of the following:

    a. At least 2 single-pool Kt/V measurements ≥1.2 on different dialysis days

    b. At least 2 urea reduction ratio measurements ≥65% on different dialysis days

c. 1 single-pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days

Open-label Extension Period

Subjects meeting all of the following inclusion criteria at the end of Week 12 of the double-blind period will enter the extension period. Subjects not meeting these inclusion criteria will be withdrawn from the study and undergo the follow-up assessments.

11. Subjects not withdrawn during the double-blind period.

12. Subjects receiving at least 30 doses of the planned 36 doses of investigational product during the double-blind period.

13. Has a prescription dry body weight ≥40 kg.

14. Continues to meet inclusion criteria 1 through 7.

15. Subjects do not have any safety or other reasons, which in the opinion of the Investigator, should exclude them from entering the open-label extension period.

5.3 Exclusion Criteria

1. Known noncompliance with dialysis treatment that in the opinion of the Investigator would impede completion or validity of the study.

2. Planned or anticipated to receive a kidney transplant during the study. Note: Being listed on a kidney transplant list is not an exclusion criterion.

3. Subjects with itching caused by conditions other than chronic renal failure or complications of chronic renal failure, which could affect the efficacy evaluation in the opinion of the Investigator (e.g., atopic dermatitis, chronic urticaria). Note: Subjects whose pruritus is attributed to ESRD complications, such as hyperparathyroidism, hyperphosphataemia, anaemia, or the dialysis procedure, or prescription may be enrolled.

4. Has localised itch restricted to the palms of the hands.

5. Has pruritus only during the dialysis session (by subject report).

6. Subjects with severe hepatic impairment (Child-Pugh Class C) or concurrent hepatic cirrhosis.

7. Subject is receiving ongoing ultraviolet B treatment and anticipates receiving such treatment during the study.

8. Subjects who previously were enrolled in any clinical study of difelikefalin and received at least 1 dose of difelikefalin.

9. Significant systolic or diastolic heart failure (e.g., New York Heart Association Class IV congestive heart failure) (Appendix 2).

10. Subjects with concurrent malignancy except excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ that has been excised or resected completely.

11. Known or suspected history of alcohol, narcotic, or other drug abuse, or substance dependence within 12 months prior to screening.

12. Severe mental illness or cognitive impairment (e.g., dementia) or other concurrent mental disorder that, in the opinion of the Investigator, would compromise the validity of study measurements.

13. Any other relevant acute or chronic medical or neuropsychiatric condition within 3 months prior to screening (e.g., diagnosis of encephalopathy, coma, delirium).

14. New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening.

15. New or change of prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening.

16. Subject is receiving prohibited medication (e.g., nalfurafine hydrochloride, opioid antagonists)

17. Subjects who received treatment with any investigational product or study device in a clinical study (including clinical studies of medical devices or cellular and tissue-based products) within 30 days prior to the informed consent procedure, or who are planning to participate in another clinical study before the end of the follow-up period of this study.

5.4 Withdrawal of Subjects

5.4.1 Withdrawal of Subjects from the Study

Subjects may voluntarily withdraw from study participation at any time without having to provide a reason. Subjects may be withdrawn because of the appearance of a new health condition requiring care or medications prohibited by the protocol, unacceptable AEs, refusal to continue treatment, major noncompliance with study procedures, significant protocol deviations, or at the Investigator's discretion if it is in the subject's best interest.

If a subject withdraws from the study at any time either at his or her request or at the Investigator's discretion, the reason(s) for withdrawal must be recorded on the relevant page of the subject's eCRF and source documentation. Subjects who withdraw from the study prematurely should undergo all end of study assessments, if possible.

If a subject is withdrawn from the study due to an AE, it is vital to obtain follow-up data. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures (see Section 10.3). If a subject is discontinued due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilisation has occurred. All AEs should be followed until resolution, stabilisation or the subject is lost to follow-up and cannot be contacted.

If a subject refuses to continue study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study-specific eCRF. Although subjects are not obliged to give a reason for withdrawing consent, the Investigator should make every effort to obtain the reason, while fully respecting the subject's rights. If the subject withdraws from the trial without providing a reason, the source documents and the eCRF should document the reason for discontinuation as "withdrawal by subject".

5.5 Rescreening of Subjects

A subject can only be randomised once in the trial. Randomised subjects who discontinue from the study after administration of the first dose of investigational product and before completing the protocol procedures will not be replaced.

- Rescreening will be considered on an individual subject basis and must be first approved by the Sponsor or designee. However, rescreening will not be permitted if a subject missed the entry criteria for itch intensity, i.e., the weekly mean of the daily 24-hour WI-NRS score <5. A subject can only be rescreened once. Rescreening can only occur after at least 2 weeks from screening.

6. STUDY TREATMENTS

6.1 Treatment Blinding

During the double-blind period, study participants, Investigators, site study staff, and the Sponsor/Contract Research Organisation (CRO) will be blinded to investigational product assignment. Treatment randomisation information will be kept confidential by an unblinded biostatistician until the study database has been locked.

Clinical trial supply management staff will have access to overall difelikefalin/placebo usage at a site level for oversight of investigational product stock levels.

If the Investigator or site study staff become aware of a subject's investigational product assignment, efforts should be made to not disclose treatment assignments to other study site staff, subjects, or their caregivers.

During the double-blind period, the blind will only be broken under the conditions specified in Section 6.1.1.

6.1.1 Treatment Unblinding

During the double-blind period, the study blind will be broken for an individual subject only in the following situations:

- For medically urgent or emergent situations that necessitate knowledge of investigational product assignment for subject management.
- When reporting of the treatment arm to the Health Authorities is required, e.g., for reporting a suspected unexpected serious adverse reaction (SUSAR) (see Section 10.7.3).
- If a subject becomes pregnant during the study, the knowledge of the treatment arm is therefore necessary (see Section 10.8.3).

Except for when subject's care requires the treatment assignment immediately, the Investigator must submit a written report, including all pertinent details, to the Medical Monitor within 24 hours of the unblinding. The Sponsor and Medical Monitor will receive a report whenever a subject blind is broken.

If breaking of the blind is required, the unblinded information should be, wherever possible, accessible only to those of site study staff who need to be involved in the diagnostic workup, treatment, or medical follow-up of the subject (e.g., in case of a medical emergency or a pregnancy), or in the safety reporting to external regulatory bodies (e.g., in case of a SUSAR or a pregnancy).

Unblinding must always be performed according to the procedures that are specified in the applicable Standard Operating Procedures effective for this study.

6.2 Dosage Forms/Formulation

All investigational products used in this study have been manufactured in accordance with current Good Manufacturing Practice and will be provided by the Sponsor.

6.2.1 Difelikefalin (IV Formulation)

Difelikefalin (IV formulation) will be provided in 2 R glass vials with an extractable volume of 1 ml of difelikefalin at a concentration of 50 µg /ml in 0.04 M isotonic acetate buffer, pH 4.5.

Active Ingredient:	Difelikefalin
Chemical Name:	4-amino-1-((R)-6-amino-2-((R)-2-((R)-2-((R)-2-amino-3-phenylpropanamido)-3-phenylpropanamido)-4-methylpentanamido)hexanoyl)piperidine-4-carboxylic acid
Abbreviated Peptide Sequence:	D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl-γ-(4-N-piperidinyl)-amino-carboxylic acid, acetate salt
Strength:	0.05 mg (free base)/ml
Excipients:	0.04 M isotonic acetate buffer, pH 4.5
Appearance:	Clear, colourless solution
Dosage Form:	Injection
Manufacturer:	Siegfried Hameln GmbH
Storage:	Do not store above 30°C. Do not freeze.

6.2.2 Placebo

Placebo will be provided in 2 R glass vials.

Content:	Acetic acid, sodium acetate trihydrate, sodium chloride, and water for injection
Appearance:	Clear, colourless solution
Dosage Form:	Injection
Manufacturers:	Siegfried Hameln GmbH or Patheon Manufacturing Services LLC
Storage:	Do not store above 30°C. Do not freeze.

6.3 Investigational Product Dosage and Administration

The investigational product will be dispensed by qualified site study staff who have received training on handling and administration of investigational product.

Individual IV doses of investigational product are based on subject body weight (0.5 µg/kg dry body weight) and prepared by withdrawing subject-specific volume of investigational product with sterile, single-use 1 ml Plastipak syringe (or equivalent) and sterile single-use needles. A single vial cannot be used for multiple subjects. Vials contain an extractable volume of 1 ml of investigational product.

The total dose volume (ml) required from the vial should be calculated as follows: 0.01 × prescription dry body weight (kg), rounded to the nearest tenth (0.1 ml). The total dose volumes per weight range are detailed in Table 3.

Table 3 Total Dose Volumes per Weight Range

Weight Range (Dry Body Weight in kg)		Dose (ml)
40	44	0.4
45	54	0.5
55	64	0.6
65	74	0.7
75	84	0.8
85	94	0.9
95	100	1.0

If the syringes are prepared using aseptic techniques, subjects must be dosed (IV bolus) within 24 hours of syringe preparation with capped syringes stored at 2°C to 8°C until use. If the syringes are not prepared using aseptic techniques (i.e., prepared under a sterile hood), subjects must be dosed within 60 minutes of syringe preparation. If the syringes are used within 60 minutes of preparation, they do not need to be kept refrigerated. No other special procedures are required for the safe handling of the solutions.

Investigational product will be administered by IV bolus injection within 15 minutes following the end of the dialysis on the scheduled investigational product administration day. Investigational product may be given either during or after rinse back of the dialysis circuit. Administration of investigational product can be done by injection into the dialysis venous line (e.g., into the venous port) or by direct injection into a vein. If the dialysis line is used, following the bolus, the venous line must be flushed with at least 10 ml of normal saline.

If any dialysis circuit trouble precludes injection through the dialysis circuit, the investigational product will be administered directly intravenously. If in exceptional cases an extra fourth dialysis session is required within the week, the investigational product will

be administered (up to 4 times weekly); if only the extracorporeal ultrafiltration method is used at this fourth dialysis session, the investigational product will not be administered.

Additional details on dose preparation and administration will be provided in the Pharmacy Manual.

6.4 Package and Labelling

Investigational product will be packaged and labelled in accordance with local regulations for investigational products.

6.5 Study Treatment Allocation

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. The subjects will receive a screening number, as allocated by the electronic data capture (EDC) system. Eligible subjects will be randomised into the double-blind period in a 1:1 ratio to receive either difelikefalin or placebo (see Section 12.3), i.e., a randomisation number will be allocated via a validated centralised procedure (IWRS).

For the open-label extension period, all eligible subjects who agree to participate to the open-label extension period will receive open-label difelikefalin.

6.6 Site Supply, Storage, Accountability

6.6.1 Site Supply

Once a site has been approved to receive investigational product, the site will be supplied with an initial stock of investigational product used in the study. The need for drug resupply will be assessed on a regular basis considering the number of subjects enrolled, and the number of subjects in screening at the site.

6.6.2 Storage

All investigational products must not be stored above 30ºC and must not be frozen. Each site should have a thermometer that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated by site personnel every workday. This log must be available for review by the Monitor during on-site monitoring visits.

Additional information on storage of the investigational product including prepared dosing syringes is provided in the Pharmacy Manual.

6.6.3 Accountability

The Investigator at each site is responsible for investigational product supplies. The Investigator will ensure that adequate records of the receipt, preparation, administration and return of the investigational product are kept and that the investigational product is used only for subjects enrolled in the study. All data regarding the investigational product

(including kit and/or batch numbers) must be recorded in the eCRF and on any other relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all drugs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to the Sponsor for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor. The decision to destroy investigational product at site must first be made by the Sponsor. If the investigational product is destroyed at site, the Investigator will forward the certificate of destruction to the Sponsor.

6.7 Drug Dose Modification

Dose modifications are not allowed in this study.

6.7.1 Procedures for Overdose

There is no information available on the effect of overdosing with difelikefalin. In an attempt to reverse this condition, an opioid antagonist such as naloxone may be considered for acute management of IV overdose although the clinical effectiveness of naloxone to antagonise the effects of difelikefalin has not been confirmed in humans. In extreme cases, dialysis may be considered for the treatment of overdose.

Any occurrence of an overdose must be communicated to the Medical Monitor and the Sponsor (see Section 10.8).

6.8 Prohibited Therapy and Concomitant Treatment

Any concomitant treatment (including traditional Chinese medicines) given for any reason during the study must be recorded on the eCRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

All prescription and non-prescription medications (e.g., over-the-counter drugs and herbal supplements) that subjects report taking during the 30 calendar days prior to the screening visit will be recorded in the eCRF as prior medications.

All drugs and therapies used after the Informed Consent Form (ICF) was signed should be recorded in the eCRF as concomitant medications.

For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units, and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit. All as needed prescriptions should be converted to reflect actual dose taken per day.

Any medication or therapy that is taken by or administered to the subject during the study must be recorded in the eCRF.

COVID-19 vaccination during study participation will be recorded as concomitant medications. Based on the mechanism of action of difelikefalin, an interaction with the COVID-19 vaccine is unlikely.

6.8.1 Concomitant Treatments

Subjects may continuously use any medication used to treat symptoms of chronic renal failure or other comorbidities at the start of the screening period without changing its dosage and administration regimen whenever possible until the end of the follow-up period. The dosage and administration of any concomitant medication may be changed for safety reasons including AEs. Any centrally acting concomitant drug should be used with caution due to possible central AEs that might confound the safety profile of difelikefalin.

6.8.1.1 Prohibited Concomitant Treatments

Between the start of the screening period and the end of the follow-up period, use of the following drugs will be prohibited:

- Other KOR agonists, e.g., nalfurafine hydrochloride
- Opioid antagonists: naloxone hydrochloride, eptazocine hydrobromide, naldemedine tosylate, etc., or mixed agonists-antagonists (e.g., buprenorphine and nalbuphine)
- Investigational products other than the investigational products described in this protocol.

6.8.1.2 Conditionally Permitted Concomitant Treatments

Between the start of the screening period and the end of the follow-up period, subjects may use the drugs listed below that have been used before the screening period without changing their dosage and administration. However, treatment with these drugs should not be initiated during the same time window defined above.

1. Drugs indicated for the treatment of itching (prescription/non-prescription) except prohibited concomitant medications
2. Drugs to treat itching including traditional Chinese medications (prescription/non-prescription) except prohibited concomitant medications
3. Moisturising drugs (prescription/non-prescription)
4. Steroids

   Note: Local steroids, such as inhalants, nasal drops, ear drops, eye drops, and eye ointments are allowed.

5. Capsaicin (topical)
6. Opioids
7. Pregabalin, gabapentin
8. Antidepressants, anxiolytics
9. Drugs formulated with any of the drugs listed above

Topical use of any prescription/non-prescription drugs listed in 1) to 5) above that are used to treat itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted (concomitant medications for local itching caused by insect stings, chilblains, contact dermatitis, etc. will not be restricted).

The use of any combination products that contain ingredients indicated for itching but are not indicated itself for itching will not be restricted.

6.8.1.3 Prohibited Concomitant Therapy

Between the start of the screening period and the end of the follow-up period, phototherapy to treat itching will be prohibited.

6.8.2 HD Conditions

Between the start of the screening period and the end of the follow-up period, the frequency of dialysis per week and the HD method may not be changed. Any temporary change in dialysis frequency or HD method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable. The HD conditions (duration of dialysis and dialyser) should not be changed whenever possible.

7. RISKS/PRECAUTIONS

7.1 Risks

In clinical studies, IV difelikefalin has been administered to 1,096 CKD subjects on HD for at least 12 weeks (3 months); of these subjects, 415 CKD subjects on HD with moderate-to-severe pruritus have been exposed to IV difelikefalin for at least 48 weeks (12 months).

The most common (≥5.0% of subjects) AEs reported from clinical studies with IV difelikefalin in subjects with CKD on HD with an incidence ≥1.0% greater compared with placebo were, in descending frequency, diarrhoea, nausea, fall, hypotension, dizziness, vomiting, abdominal pain, hyperkalaemia, headache, pneumonia, dyspnoea, constipation, somnolence, pyrexia, and blood thyroid stimulating hormone decreased.

Risk of Driving and Operating Machinery

Dizziness, somnolence, and mental status changes have occurred in subjects taking IV difelikefalin. IV difelikefalin may impair the mental or physical abilities needed to perform potentially hazardous activities, such as driving a car and operating machinery. Subjects should be advised not to drive or operate dangerous machinery until the effect of IV difelikefalin on a subject's ability to drive or operate machinery is known.

Dizziness, Somnolence, Mental Status Changes, and Gait Disturbances

Dizziness, somnolence, mental status changes, and gait disturbances, including falls, have occurred in subjects taking IV difelikefalin and may subside over time with continued treatment.

Somnolence (including MedDRA PTs of somnolence and sedation) and mental status changes (including MedDRA PTs of mental status changes and confusional state) have been reported as serious ADRs, with frequencies of 0.12% and 0.17%, respectively, in subjects being treated with difelikefalin during clinical developmental (including the indication for treating pruritus; N=3,478).

The incidence of somnolence was higher in IV difelikefalin-treated subjects (in the Phase3 studies) ≥65 years of age (7.0%) than in IV difelikefalin-treated subjects <65 years of age (2.8%). Concomitant use of centrally acting depressant medications, sedating antihistamines, and opioid analgesics may increase the likelihood of these adverse reactions and should be used with caution during treatment with IV difelikefalin.

7.2 Precautions

Aquaresis is defined as the increase in urinary water excretion with the sparing of electrolytes, which can result in dehydration, hypotension, tachycardia, and increases in serum sodium.

Aquaresis may be observed in subjects with normal renal function. The increases in serum sodium in difelikefalin-treated subjects with normal renal function have been generally dose-related, transient, and clinically asymptomatic.

In CKD subjects on HD, the aquaretic effects of difelikefalin do not apply due to insufficient functioning of nephrons.

7.2.1 Drug Interactions

The nonclinical data suggest that difelikefalin should possess minimal to no drug-drug interaction potential in humans. However, the effects of other drugs on difelikefalin kinetic parameters have not been evaluated.

7.2.2 Drug Abuse and Dependency

Difelikefalin has been shown to have a low to no risk to induce drug-seeking behaviour in humans. Based on clinical data including dedicated physical dependence studies conducted in humans and rodents, it can be concluded that difelikefalin has very low to no physical dependence potential.

7.2.3 Women of Childbearing Potential

Women of childbearing potential can only be enrolled in the study if:

- They are surgically sterile
- Have been amenorrhoeic for at least 1 year and are over the age of 55 years
- Have a negative serum pregnancy test within 7 days before first dose of investigational product, and agree to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after dosing

  Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed.

7.2.4 Pregnancy and Lactation

Safety and efficacy of difelikefalin have not been established in pregnant women. Although difelikefalin does not affect embryonic development in animal models, pregnant women cannot be enrolled in this study.

Safety and efficacy of difelikefalin have not been established in nursing mothers. Animal data indicate that difelikefalin is secreted into breast milk. Therefore, difelikefalin may only be administered after breastfeeding is discontinued and nursing mothers cannot be enrolled in this study.

8. STUDY ASSESSMENTS AND PROCEDURES

For a detailed schedule of assessments and procedures (including all protocol required assessments, visits and visit windows) please refer to Table 1.

8.1 Allowed Adaptations in Case of Extraordinary Events, e.g., COVID-19

The guidance below is intended for subjects who have been successfully enrolled into the study and who are unable to attend in person clinic visits due to COVID-19 restrictions. Every reasonable effort should be made to ensure that the subject continues on the study per-protocol. Study visits which coincide with dialysis days should be conducted on-site. In the event that a subject cannot come to the clinic after baseline visit due to self-quarantine, local restrictions, or illness, a visit at another local hospital may be considered.

If the subject misses, or is expected to miss, 2 consecutive clinic visits due to COVID-19, the Investigator must contact the Medical Monitor to discuss discontinuation of the subject from the study. In either scenario, the subject should return to the clinic for assessment at their earliest convenience. If it is determined that the subject must be discontinued, the reason for termination should be documented as 'related to COVID-19' under Reason for Termination: Other in the eCRF.

Extraordinary events may call for specific measures to maintain subject safety and guarantee conduct of clinical investigations according to established general and specific guidelines and regulations to meet agreed regulatory, quality, and scientific expectations.

For this, the following adaptations are considered for specific situations:

- Site visits are not possible within the defined time window, possibly leading to delayed visit:
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring.
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing.
  - AE/SAE/special situation reporting: frequent phone call visits.
- Site visits are not possible within the defined time window, possibly leading to no visit:
  - Vital signs: consultation by local physician, follow-up clinical assessment via phone remote visits at subject's home (e.g., home nursing).
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring.
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing.

- AE/SAE/special situation reporting: frequent phone call visits.

8.2 Screening Visit (Day -28 to Day -7)

The screening visit is to occur 28 to 7 calendar days before the start of treatment; it should be on a dialysis day (for assessments to be performed pre-dialysis). Sites have the option to conduct the screening visit during the run-in period (within 7 days before start of treatment) at the discretion of the Investigator.

After the subject has signed the ICF, the following assessments will be performed and recorded in the subject's source documentation/medical record and on the eCRF:

- Dispense subject identification card
- Eligibility criteria
- Demographics
- Medical history/prior medications (including antipruritic medications)
- Physical examination
- Prescription dry body weight
- 12-lead ECG obtained before starting dialysis
- Vital signs (body temperature, heart rate, and blood pressure) obtained before starting dialysis with the subject in a sitting or semi-recumbent position
- Samples for serum chemistry (for central laboratory assessment) obtained before starting dialysis to include:
  - Albumin, alkaline phosphatase (AP), ALT, AST, bilirubin (total), BUN, creatinine, glucose
  - Electrolytes (calcium, chloride, phosphorus, potassium, and sodium)
- Haematology obtained before starting dialysis to include basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, haemoglobin (Hb), lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, red blood cells (RBCs), white blood cells (WBCs). Assessment to be performed via central laboratory
- Serum pregnancy in women of childbearing potential (central laboratory assessment) within 7 days prior to the first dose of investigational product
- AEs assessment

8.3 Run-in Period (Day –7 to Day -1)

Eligible subjects will complete a 7-day run-in period before randomisation to confirm that each subject has moderate-to-severe pruritus (i.e., weekly average worst itch score ≥5), as measured by the subject-daily reported 24-hour WI-NRS, and to establish a baseline itch intensity. Subjects must not be informed that they need to report a weekly average worst itch score ≥5 to be enrolled in the study.

The following assessments/events will take place during the run-in period:

- Medical history/prior medications (including antipruritic medications). Medical history will be updated on Day 1 with any changes since the screening visit, and inclusion/exclusion criteria will be confirmed prior to randomisation. Antipruritic medication will be updated at each dialysis visit during the run-in period
- WI-NRS questionnaire
  - During the first visit (Day -7) of the run-in period, subjects will be trained on completion of the 24-hour WI-NRS
  - Subjects will start the reporting of their WI-NRS daily score on Day −7 until Day −1. For consistency, subjects will be requested to complete the NRS worksheets (either at home or in the dialysis unit, as required) each day at a similar time of day around the normal start time of their dialysis.
- Subject training on PRO worksheets. Training on Skindex-10 scale and 5-D itch scale may be performed at any time during the week prior to randomisation or at the latest on Day 1 of the double-blind period
- AEs assessment
- Structured safety evaluation: A list of specific signs/symptoms will be verified with the subject by qualified site study staff, preferably to be completed on Wednesday/Thursday (not to be completed on Monday/Tuesday)

8.4 Double-blind Period

If subjects continue to meet all inclusion and no exclusion criteria at the end of the 7-day run-in period, they will be randomised on Day 1 into the double-blind period in a 1:1 ratio to receive either difelikefalin or placebo. Subjects will be stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to randomisation (run-in period) as well as the presence or absence of specific medical conditions (See Section 12.3).

Each visit during the double-blind period will coincide with the subject's normal dialysis treatments.

8.4.1 Week 1/Day 1

Day 1 of the double-blind period will be defined as the day of administration of the first dose of investigational product and will occur preferably on the first dialysis session of the first treatment week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule). Subjects will be administered investigational product after the end of each dialysis session during the 12-week double-blind period. Each subject is to receive investigational product 3 times weekly for a total of 36 doses.

The following assessments and procedures will be performed on Day 1:

- Medical history/prior medications; medical history will be updated with any changes since the screening visit
- Confirm eligibility criteria before randomisation
- Randomisation
- Prescription dry body weight
- Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, to be assessed when the subject is in a sitting or semi-recumbent position
- Samples for serum chemistry (central laboratory assessment) obtained before starting dialysis to include:
  - Albumin, AP, ALT, AST, bilirubin (total), BUN, creatinine, glucose
  - Electrolytes (calcium, chloride, phosphorus, potassium, and sodium)
- Haematology samples (central laboratory assessment) obtained before starting dialysis to include basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, Hb, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, RBCs, WBCs
- Subject training on PRO worksheets (Skindex-10 scale and 5-D itch scale) if not done previously during the week before randomisation
- WI-NRS questionnaire
  - Subjects can complete the questionnaire before or during dialysis but before dosing
  - Remind subjects to complete the questionnaire daily at home on non-dialysis days around the normal start time of their dialysis

- Subjects to complete 5-D itch scale (preferably first) and Skindex-10 scale. If the first visit of the week is missed, the subject may complete the worksheets at their next visit for the same week. The questionnaires could be completed before or during dialysis (preferably within 1 hour of the dialysis) but before dosing

- IV administration of investigational product within 15 minutes after completion of dialysis session

- AEs assessment

- Concomitant medications (including antipruritic medications)

8.4.2 Week 1/Day 3

- WI-NRS questionnaire

  - Subjects can complete the questionnaire before or during dialysis but before dosing

  - Remind subjects to complete the questionnaire daily at home on non-dialysis days around the normal start time of their dialysis

- IV administration of investigational product within 15 minutes after completion of dialysis session

- AEs assessment

- Concomitant medications (including antipruritic medications)

- Structured safety evaluation: A list of specific signs/symptoms will be verified with the subject by qualified site study staff

8.4.3 Week 1/Day 5

- WI-NRS questionnaire

  - Subjects can complete the questionnaire before or during dialysis but before dosing

  - Remind subjects to complete the questionnaire daily at home on non-dialysis days around the normal start time of their dialysis

- IV administration of investigational product within 15 minutes after completion of dialysis session

- AEs assessment

- Concomitant medications (including antipruritic medications)

8.4.4 Week 2 to Week 12

- Record vital signs Week 3/Day 15, Week 5/Day 29, Week 7/Day 43, Week 9/Day 57 and Week 11/Day 71
  - Vital signs include body temperature, heart rate, and blood pressure
  - Assess before dialysis with the subject in a sitting or semi-recumbent position
  - Measure heart rate at each dialysis; if heart rate is clinically significant at visits outside the pre-specified visits per Table 1, the heart rate will be recorded in the eCRF
- Serum potassium assessment at Week 3/Day 15, Week 5/Day 29, Week 7/Day 43, Week 9/Day 57 and Week 11/Day 71 (central laboratory)
- WI-NRS questionnaire to be completed daily (from Week 2 to Week 12)
- Subjects can complete the questionnaire before or during dialysis but before dosing
  - Remind subjects to complete the questionnaire daily at home on non-dialysis days around the normal start time of their dialysis
- Subjects to complete 5-D itch scale (preferably completed first) and Skindex-10 on the first visit of Week 5/Day 29 and of Week 9/Day 57. If the first visit of the week is missed, the subject may complete the worksheets at their next visit for the same week. The questionnaires can be completed before or during dialysis (preferably within 1 hour of the dialysis) but before dosing
- IV administration of the investigational product (3 times a week within 15 minutes after completion of the dialysis sessions)
- AEs assessment
- Concomitant medications (including antipruritic medications) to be recorded at each dialysis visit
- Structured safety evaluation: A list of specific signs/symptoms will be verified with the subject by qualified site study staff, preferably to be completed on Wednesday/Thursday each week during the double-blind period (not to be completed on Monday/Tuesday)

8.5 Double-blind Period End of Treatment/Early Termination/Day 85

On completion of the double-blind period (i.e., last study visit Day 85), or if subject is discontinued/withdrawn early, the following assessments and procedures should be performed:

- 12-lead ECG obtained before starting dialysis
- Vital signs (body temperature, heart rate, and blood pressure) obtained before starting dialysis with the subject in a sitting or semi-recumbent position
- Samples for serum chemistry (central laboratory assessment) obtained before starting dialysis to include:
  - Albumin, AP, ALT, AST, bilirubin (total), BUN, creatinine, glucose
  - Electrolytes (calcium, chloride, phosphorus, potassium, and sodium)
- Haematology samples (central laboratory assessment) obtained before starting dialysis to include basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, Hb, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, RBCs, WBCs
- Serum pregnancy in women of childbearing potential (central laboratory assessment)
- Subject training on PRO worksheet Patient Global Impression of Change
- WI-NRS questionnaire
  - Subjects can complete the questionnaire before or during dialysis but before dosing
  - Remind subjects to complete the questionnaire daily at home on non-dialysis days around the normal start time of their dialysis
- Subjects to complete 5-D itch scale (preferably first) and Skindex-10 scale. If the first visit of the week is missed, the subject may complete the worksheets at their next visit for the same week. The questionnaires could be completed before or during dialysis (preferably within 1 hour of the dialysis) but before dosing
- Patient Global Impression of Change
- AE assessment
- Concomitant medications (including antipruritic medications)

Note: The end-of-treatment visit in the double-blind period will be the first dialysis visit following the last dose of investigational product, i.e., first dialysis on Week 13/Day 85, which also corresponds to Day 1 of the open-label extension period.

8.6 Follow-up Period (ONLY for Subjects not Participating in the Open-label Extension Phase)/Day 85 to Day 95

- Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, will be recorded at the follow-up visit (at 7 to 10 days after end-of-treatment/early termination visit). Heart rate will be measured at each dialysis visit during the follow-up period; if heart rate is clinically significant at visits outside the follow-up visit, the heart rate will be recorded in the eCRF

- WI-NRS worksheets to be completed only on dialysis days

- AEs assessment

- Concomitant medications

- Structured safety evaluation: A list of specific signs/symptoms will be verified with the subject by qualified site study staff once during the follow-up period

8.7 Open-label Extension Period

Subjects who received at least 30 doses of investigational product during the 12-week double-blind period and continue to meet other eligibility criteria will be eligible to receive open-label difelikefalin for an additional 14 weeks. Each subject will receive difelikefalin at a dose of 0.5 μg/kg after the end of each dialysis session, 3 times per week for up to 14 weeks, regardless of whether they had been previously administered placebo or difelikefalin. Prescription dry body weight will be recorded at the start of the open-label extension phase; if there is a ±10% or more change from the prescription dry body weight recorded at screening, then the difelikefalin dose will be adjusted according to the newly recorded dry body weight.

8.7.1 Day 1/Open-label Extension

The first visit and first dosing for the open-label extension phase of the study will occur immediately on the day of the last visit of the double-blind period or up to 1 week following the double-blind treatment period.

The following assessments will be performed:

- Eligibility criteria assessment for entry into the open-label phase

- Physical examination

- Prescription dry body weight to be captured from the dialysis prescription. If there is a >10% change in prescription dry body weight compared to the last value, then the difelikefalin dose will be adjusted

- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis
- IV administration of difelikefalin (within 15 minutes after completion of dialysis sessions)
- AEs assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.2 Week 2/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. The following assessments will take place:

- Assessment of serum potassium before starting of dialysis (central laboratory)
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.3 Week 4/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. The following assessments will take place:

- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate will be measured at each dialysis; if the heart rate is clinically significant at visits outside the pre-specified visits per Table 2, the heart rate will be recorded in the eCRF
- Assessment of serum potassium before starting of dialysis (central laboratory)
- Subjects to complete 5-D itch scale and Skindex-10 scale before or during dialysis (preferably within 1 hour of the dialysis but before dosing). 5-D itch scale will preferably be completed first.
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis

- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.4 Week 6/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. The following assessments will take place:

- Assessment of serum potassium before starting of dialysis (central laboratory)
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.5 Week 8/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week if all assessments are completed during that visit. The following assessments will take place:

- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate will be measured at each dialysis; if the heart rate is clinically significant at visits outside the pre-specified visits per Table 2, the heart rate will be recorded in the eCRF
- Assessment of serum potassium before starting of dialysis (central laboratory)
- Subjects to complete 5-D itch scale and Skindex-10 scale before or during dialysis (preferably within 1 hour of the dialysis but before dosing). 5-D itch scale will preferably be completed first
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.6 Week 10/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week as long as all assessments are completed during that visit. The following assessments will take place:

- Assessment of serum potassium before starting of dialysis (central laboratory)
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.7 Week 12/Open-label Extension

The study visit may occur on any chosen dialysis day of a scheduled week if all assessments are completed during that visit. The following assessments will take place:

- Prescription dry body weight to be captured from the dialysis prescription. If there is a >10% change in prescription dry body weight compared to the last value, then the difelikefalin dose will be adjusted
- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate will be measured at each dialysis; if the heart rate is clinically significant at visits outside the pre-specified visits per Table 2, the heart rate will be recorded in the eCRF
- Assessment of serum potassium before starting of dialysis (central laboratory)
- Subjects to complete 5-D itch scale and Skindex-10 scale before or during dialysis (preferably within 1 hour of the dialysis but before dosing). 5-D itch scale will preferably be completed first
- IV administration of difelikefalin (within 15 minutes after completion of dialysis session)
- AE assessment on an ongoing basis
- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.8 First Dialysis of Week 15/Open-label Extension End of Treatment/Early Termination

The end-of-treatment visit will be the first dialysis visit following the last dose of investigational product (i.e., first dialysis on Week 15). The following assessments will be performed:

- Pre-dialysis 12-lead ECG

- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis

- Samples for serum chemistry (central laboratory assessment) obtained before starting dialysis to include:

  – Albumin, AP, ALT, AST, bilirubin (total), BUN, creatinine, glucose

  – Electrolytes (calcium, chloride, phosphorus, potassium, and sodium)

- Haematology samples (central laboratory assessment) obtained before starting dialysis to include basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, Hb, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, RBCs, WBCs

- Serum pregnancy test for women of childbearing potential only (central laboratory assessment)

- 5-D itch scale and Skindex-10 scale (to be completed in the dialysis unit at any time before or during dialysis)

- AE assessment on an ongoing basis

- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

8.7.9 Follow-up for Subjects Participating in the Open-label Period

A follow-up visit will be performed 7 to 10 days after end of treatment/early termination on a dialysis day. The following assessments will take place:

- Pre-dialysis vital signs (body temperature, heart rate, and blood pressure) to be obtained while the subject is in a sitting or semi-recumbent position prior to the start of dialysis

- AE assessment on an ongoing basis

- Concomitant medications (including antipruritic medications) recorded on an ongoing basis

9. STUDY ASSESSMENTS

All assessments will be performed as noted in the Schedule of Events (Table 1).

9.1 Demographics and Medical/Surgical History

Subject's demographics (gender, age, and race) and baseline characteristics including prescription dry body weight, and medical history will be taken during the screening visit.

Information to be collected will include the aetiology and clinical presentation of CKD and CKD-related events (e.g., pruritus, CKD-mineral and bone disorder, secondary hyperparathyroidism), and the date when CKD was first diagnosed, and other clinically relevant past and present medical conditions which were diagnosed/occurred before signing the informed consent and/or for which the subject is currently treated. Any history of alcohol, narcotic, or other drug abuse or dependence within 12 months before screening will be collected.

All medications and treatments prescribed at the time of informed consent must be documented on the appropriate eCRF pages. In addition, treatments prescribed up to at least 3 months before obtaining the informed consent must be documented in the eCRF, irrespective if the treatment is still ongoing at the time of screening. All changes to or addition of concomitant treatments as of informed consent must be recorded (including changes in dose, change in formulation, starting or stopping medications) in the eCRF. If the indication for changing a subject's concomitant treatment constitutes a new medical condition or a worsening of an existing clinical condition which is considered by the Investigator as being clinically relevant, the indication must be documented as an AE (see Section 10).

9.2 Physical Examination and Vital Signs

Physical examination will include general appearance, cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin. Any findings at screening should be reported in the medical history; clinically significant changes should be reported as AEs.

Vital signs will include oral body temperature (°C), respiratory rate, radial pulse rate, systolic and diastolic blood pressures. Sitting recordings are to be made after the subject has been sitting for at least 5 minutes with their feet squarely on the floor and arms relaxed, bent at the elbow.

An AE form must be completed for all changes identified as clinically noteworthy.

9.3 12-lead ECG

Standard 12-lead ECGs will be measured after the subject has been resting for minimum of 5 minutes.

All 12-lead ECG recordings (including heart rate, QT, QTcF, QTcB, RR interval, P-wave, QRS complex duration and PR interval) will be performed and interpreted at study sites by Investigators. ECGs will be planned to coincide with first dialysis of the week. If this is not possible, ECGs should be planned for the same session of the week.

At screening, the Investigator must document clinically relevant ECG findings on the appropriate baseline eCRF pages and in the subject's hospital records. Any new clinically relevant ECG finding, or aggravation/worsening of an already existing finding as assessed by the Investigator, must be reported as an AE (see Section 10).

9.4 Clinical Laboratory Tests

The following clinical laboratory tests are to be performed via central laboratory as indicated in the Schedule of Events (Table 1 and Table 2).

- Serum chemistry:
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, creatinine, BUN
  - Electrolytes (sodium, potassium*, chloride, calcium, and phosphorus)
- Haematology:
  - Basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, Hb, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, RBCs, WBCs
- Other:
  - Serum pregnancy test in women of childbearing potential

*Serum potassium will be additionally assessed at time points as noted in the Schedule of Events (Table 1 and Table 2).

Details on the processing and shipment of specimens are provided in the Laboratory Manual. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Details on the clinical laboratories used in this clinical trial, such as address, accreditation certificates, are available in the Trial Master File.

9.5 Adverse Events

See Section 10.

9.6 Prior, Concomitant, and Prohibited Medications

Prior medications (including over-the-counter drugs and herbal supplements reported by the subjects) are defined as prescription and non-prescription medications taken any time during the last 3 months prior to the first dose of investigational product (Day 1 of the double-blind period) and ending before Day 1.

Concomitant medications are defined as all drugs and therapies used on Day 1 of the double-blind period or after the first dose of the investigational product on Day 1 and through the end of the follow-up period.

Use of antipruritic medications during the study will be recorded on an ongoing basis, starting at screening. Subjects having a prescription for the use of anti-itch medication will be stratified as using anti-itch medication even if such medications were not reported to be used during the run-in period. Medications known for potential antipruritic effects but used for a different indication (e.g., use of gabapentin for pain management) will not be reported as antipruritic medications.

All prior and concomitant medications, including over-the-counter medications used by subjects during this study, are to be recorded in the appropriate page of the eCRF, as applicable.

For a list of conditionally permitted concomitant treatment see Section 6.8.1.2.

For a list of prohibited concomitant treatment see Section 6.8.1.1.

COVID-19 vaccination during study participation will be recorded as concomitant medications. Based on the mechanism of action of difelikefalin, an interaction with the COVID-19 vaccination or an impact of the vaccination on difelikefalin are unlikely.

9.7 PRO Measures

The effect of difelikefalin on itch will be measured by means of the following PRO measures:

- WI-NRS score
- Skindex-10 scale
- 5-D itch scale

Patient Global Impression of Change Subjects will be trained on completion of the WI-NRS scale before the first visit of the run-in period and will be trained on the other itch-related PRO measures at any time before Day 1 of the double-blind period. All questionnaires must be completed in strict adherence to the training manual for patient reported assessments.

9.7.1 WI-NRS

Intensity of itch will be measured using an NRS scale (Appendix 1) on a worksheet on which subjects will be asked to indicate the intensity of the worst itching they have experienced over the past 24 hours by marking one of 11 numbers, from 0 to 10, that best describes it, where 0 is labelled with the anchor phrase "no itching" and "10" is labelled "worst itching imaginable." Subjects will be provided with the WI-NRS worksheets to record their 24-hour worst itching assessment scores, both at the clinic on dialysis days and at home on non-dialysis days.

The WI-NRS has been widely utilised for evaluation of chronic itch, including uraemic pruritus [15-18].

9.7.2 Skindex-10 Scale

Developed specifically for uraemic pruritus, the Skindex-10 scale (Appendix 3) is an instrument for measurement of QoL that correlates with itch intensity [17]. Subjects are asked to mark 1 of 7 boxes numbered from 0 (labelled with the anchor phrase "never bothered") to 6 (labelled as "always bothered") for each of the 10 questions describing how often they have been bothered by their itch and its impact over the past week. The total score is the sum of the numeric value of each answered question. The total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

9.7.3 5-D Itch Scale

The 5-D itch scale was developed as a brief, multidimensional questionnaire designed to be useful as an outcome measure in clinical studies. The 5 dimensions of itch assessed are degree, duration, direction, disability, and distribution (Appendix 4). Subjects are asked to mark boxes that best describe the impact of their itch over the past 2 weeks. The scale has been validated in patients with chronic pruritus, including HD patients and has been shown to be sensitive to changes in pruritus over time [19].

9.7.4 Patient Global Impression of Change

The Patient Global Impression of Change is a global PRO measure that assesses the change in itch (no change, improvement or worsening) overall relative to the start of the study [20]. The scale has only 1 item, and the subject is asked to mark the category that best describes the change in itch ranging from "Very Much Improved" to "Very Much Worse" (Appendix 5).

10. EVALUATION, RECORDING, AND REPORTING OF AEs

10.1 Definition of AEs

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational product.

10.2 AE Reporting Period

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at the last study visit (end of study/early termination). For SAE reporting period, see Section 10.7.2.

10.3 Eliciting AEs

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

10.4 Assessing AEs

10.4.1 Intensity/Severity

The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating, and the subject is unable to work or complete usual activity.

Every change in intensity of a particular AE experienced by the subject during the course of the event is recorded.

It is important to note the distinctions between severe AEs and SAEs. Severity is a classification of intensity of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such

as severe headache). An SAE, however, is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 10.7.1 (i.e., a headache may be severe, interferes significantly with subject's usual function, but would not be classified as serious unless it met 1 of the criteria for SAEs).

10.4.2 Causality and Reporting

An Investigator who is qualified in medicine must make the determination of relationship to investigational product for each AE and SAE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product.

If there is no valid reason for suggesting a relationship, then the AE/SAE should be classified as unrelated or unlikely related and an alternative suspected aetiology should be provided if available (i.e., concomitant medications, intercurrent illness/events). Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered certainly, probably/likely, or possibly related.

The following additional guidance may be helpful:

Term	Relationship	Definition
Certain	Yes	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	No	• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanation
Unrelated	No	• Event or laboratory test abnormality which is clearly related to circumstances not connected with the drug intake

If the causal relationship between an AE/SAE and the investigational product is determined to be “certainly, probably/likely, or possibly related”, the event will be considered to be

related to the investigational product for the purposes of expedited regulatory reporting. In circumstances where the causal relationship has not been provided, the event will be considered as related and qualify for expedited regulatory reporting.

10.4.3 Outcome Categorisation

Outcome may be classified as: recovered/resolved (i.e., without sequelae); recovered/resolved with sequelae; recovering/resolving; not recovered/not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

“Fatal” should be recorded as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for the AE that, in the opinion of the Investigator, is the most plausible cause of death. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and an autopsy report should be provided where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

Although “fatal” is usually an outcome of an event, events such as sudden death or unexplained death should be reported as SAEs.

10.5 Recording and Reporting

10.5.1 Persistent or Recurrent AEs

AEs that extend continuously, without resolution, between trial assessments should only be recorded once in the eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens.

AEs that resolve and subsequently recur should have each recurrence recorded separately in the eCRF.

All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject’s source documents.

10.5.2 Diagnosis Versus Signs and Symptoms

Where possible, the Investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

10.5.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the medical history eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.5.4 Clinical Laboratory Evaluations

Not every out-of-range laboratory result qualifies as an AE. A laboratory investigation result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Presents shift of a parameter from a normal value to a pathological value, or results in a deterioration of common toxicity criteria grade, or a further worsening of an already pathological value
- Is clinically significant in the Investigator’s judgement

It is the Investigator’s responsibility to review all laboratory findings. Medical and scientific judgement should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product,

and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.7.1), it must be reported as an SAE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”).

If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE, for example, hypercalcaemia or hypoglycaemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

All pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.5.5 Worsening of the Disease Under Study

Symptoms and signs of the disease under study should not be considered AEs as long as they are not regarded as worsening of the clinical features of the disease under study. If a sign or symptom of the disease has unexpectedly worsened in severity or frequency or changed in nature at any time during the study, the symptoms and signs should be recorded as AEs, and clearly marked as worsening of the signs or symptoms in the eCRF.

10.5.6 Abnormal Vital Signs and Other Abnormalities

Not every abnormal vital sign, ECG, or other safety assessment qualifies as an AE. A result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms or lead to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE)

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention, a change in concomitant therapy, or subject referral for further testing outside the protocol

- Clinically significant abnormality in the Investigator's judgement

It is the Investigator's responsibility to review all vital signs, ECG, and other safety findings. Medical and scientific judgement should be exercised in deciding whether an isolated abnormality should be classified as an AE.

If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the eCRF.

Observations of the same clinically significant abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.6 ADR and Reference Safety Information

10.6.1 Adverse Drug Reaction

An ADR is a response to a medical product (any dose administered). A causal relationship between an investigational product and an AE is at least a reasonable possibility. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs judged as having a reasonable causal relationship to an investigational product will be designated as ADRs.

10.6.2 Reference Safety Information

The Reference Safety Information presents the basis for expectedness assessment of an adverse reaction for expedited reporting and annual safety reporting, as well as surveillance of subject's safety in a clinical trial by regulatory (and ethic) bodies.In the context of this study, the Reference Safety Information is integrated in the latest version of difelikefalin IB.

10.7 Serious Adverse Event

10.7.1 Definition of SAE

An SAE is defined as any untoward medical occurrence that either:

- Results in death

- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)

- Requires inpatient hospitalisation or prolongation of existing hospitalisation (unless elective surgery (a planned, non-emergency medical procedure))

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

- Is an important medical event (i.e., medically significant)

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events should also be considered as serious.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

Any suspected transmission of any infectious agent via a medicinal product should be considered as an important medical event (i.e., medically significant) and therefore documented as an SAE.

The Investigator is encouraged to discuss with the Sponsor (or its delegate, e.g., CRO) any AEs for which the issue of seriousness is unclear or questionable.

10.7.1.1 Situations that are Not Considered SAEs

The following situations are not considered as SAEs:

- Visits to the emergency room or hospital department that do not result in a hospital admission lasting more than 24 hours

- Elective or pre-planned surgery for a pre-existing condition that has not worsened

- Routine health assessments requiring admission not associated with any deterioration in condition

- Social admission (lack of housing, family circumstances, etc.)

- A planned overnight stay for logistical reasons only prior to investigational product administration does not fulfil the criteria of an SAE unless there is also a medical reason for the admission

10.7.2 SAE Reporting

The SAE reporting period begins at the time the ICF is signed by the subject. The SAE reporting period ends 30 days following the last study visit or until 30 days after last investigational product administration, whichever is longer. After last study visit, SAEs that comes to the attention of the Investigator must be reported to the CRO/Sponsor and will be documented in the safety database of the Sponsor only and not in eCRF.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study visit or until 30 days after the last investigational product administration, whichever is longer, whether considered treatment-related or not, must be reported to the Sponsor (or its delegate, e.g., CRO).

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after database lock of the clinical database will be documented in the safety database and implications for handling the data in the clinical database assessed on an individual case basis.

The occurrence of an SAE must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness by using the study-specific Sponsor SAE form/via SAE CRF/eCRF in the EDC, or as defined in the study monitoring plan. This includes all SAEs (independent of relationship to study treatment).

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious (i.e., met at least 1 of the criteria for seriousness; see Section 10.7.1). If the condition started as a non-serious event and then became serious, 1 AE and 1 SAE will be recorded. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable.

10.7.3 Suspected Unexpected Serious Adverse Reaction

The definition of a SUSAR is any ADR (see Section 10.6.1) that is both serious (see Section 10.7.1) and unexpected (per the Reference Safety Information; see Section 10.6.2) that, based on the opinion of the Investigator or Sponsor, is felt to have a reasonable possibility or suspected causal relationship to an investigational product.

10.7.3.1 SAE Expedited Reporting

The Sponsor will notify all Investigators of all SAEs requiring expedited reporting to Regulatory Authorities.

The Investigator is responsible for notifying the Independent Ethics Committee (IEC) in accordance with local regulations of all SAEs that occur. The Investigator must review and file the safety report with the difelikefalin IB.

10.8 Special Situations

10.8.1 Definition of Special Situations

The following are defined as special situations:

- Use of an investigational product during pregnancy or breastfeeding
- Use of an investigational product in a paediatric or elderly population (if this is not the population under investigation)
- Medication error: any unintentional error in the prescribing, dispensing or administration of an investigational product during the study
- Medication misuse: an intentional and inappropriate use of an investigational product not in accordance with the protocol dose, route of administration, and/or the indication(s)
- Medication overdose: the administration of a quantity of investigational product given per administration, which is above the protocol maximum permitted dose
- Drug interaction involving investigational product
- Unexpected therapeutic or clinical benefit from investigational product use

Suspected AEs associated with medication errors of the investigational product or use outside that foreseen in the protocol (e.g., overdose,) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study-specific documentation.

10.8.2 Special Situation Recording and Reporting

All special situations have to be documented in the subject's eCRF and source documents. The Investigator should also complete and submit the Sponsor paper Special Situation form immediately (i.e., within 24 hours of awareness) to the Sponsor, following the same procedure as for SAEs (Section 10.7.2).

If any special situation leads to an SAE (see Section 10.8.1), then the event must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness using the study-specific Sponsor SAE form/via SAE CRF/eCRF in EDC.

10.8.3 Pregnancy Exposure and Birth Events

10.8.3.1 Definition of Pregnancy Exposure and Birth Events

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per-protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal

births) must be followed up and documented, even if the subject was withdrawn from the study or the study has been completed.

Women of childbearing potential, defined as a premenopausal female capable of becoming pregnant, should have a negative serum pregnancy test within 7 days before first dose of investigational product is administered and at the end of study treatment (Day 8). Investigational product should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained. As per inclusion criteria, women of childbearing potential must agree to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after dosing. Please also refer to the eligibility criteria (Section 5).

Per inclusion criteria, male subjects will agree not to donate sperm from investigational product administration until 7 days after the dosing and will agree to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after investigational product administration.

A female subject must immediately inform the Investigator if she becomes pregnant during the study and be instructed to stop taking investigational product. The Medical Monitor must be contacted immediately to break the blind (if applicable). The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

10.8.3.2 Pregnancy Exposure and Birth Events Recording and Reporting

Any report of pregnancy recorded for any female subject or for a female partner of a male subject should be reported to the Sponsor (or its delegate, e.g., CRO) within the same timelines as an SAE, i.e., immediately (within 24 hours of awareness). The outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was discontinued from the study. Complications of pregnancy such as abortion (spontaneous or induced), premature birth (before 37 weeks gestational age) or congenital abnormality are considered SAEs and should be reported using the study-specific Sponsor SAE form.

All pregnancies occurring in a female subject or the female partner of a male subject within 90 days after discontinuation of the investigational product should be reported within the same timelines as a SAE to the Sponsor (or its delegate, e.g., CRO).

10.8.4 Adverse Events of Special Interest

10.8.4.1 Definition of AESIs

An AESI is a medical occurrence specific to the product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. Such an event, depending on the nature and the outcome, may be serious (see Section 10.7.1) or non-serious.

Based upon results of the studies in the HD population, the following categories (MedDRA PT) were identified as AESIs for the HD population:

- Gait disturbance (gait disturbance)
- Falls (fall)
- Dizziness (dizziness)
- Somnolence (somnolence)
- Seizures (seizure)
- Syncope (syncope)
- Mental status changes (mental status changes)
- Mood changes (mood altered)
- Unusual feeling/sensation (feeling abnormal)
- Tachycardia (sinus tachycardia, tachycardia, and tachyarrhythmia)
- Palpitations (palpitations)

10.8.4.2 AESI Reporting and Recording

AEs classified as AESIs will be noted in the AE section of the subject's eCRF and source documentation. Any AESI satisfying any of the criteria for seriousness should be reported using the study-specific Sponsor SAE form/via SAE CRF/eCRF in EDC. The Investigator should notify the Sponsor immediately (i.e., within 24 hours of awareness), following the same procedure as for SAEs (Section 10.7.2).

11. DATA AND SAFETY MONITORING BOARD/DATA MONITORING COMMITTEE PROCEDURES

An independent Data and Safety Monitoring Board/Data Monitoring Committee will not be established for this study.

12. STATISTICAL ANALYSIS

12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute Inc. SAS/STAT, Cary, NC, US). The level of significance to be used will be set an alpha of 0.05 (2-sided). Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP, which will be finalised prior to database lock. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the final study report.

Frequency tables for categorical variables (absolutes and relative frequencies) and descriptive statistics for continuous variables (i.e., number of subjects, mean, SD, minimum, median, quartiles, and maximum) will be calculated.

12.2 Sample Size and Power Calculations

Double-blind Period

In a Japanese Phase 2 clinical study (MR13A9-4), a mean difference of –1.0 was observed between the difelikefalin and placebo groups with an SD of 2.09 and 1.98 in the difelikefalin and placebo group, respectively, regarding the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at end of Week 4.

In the pooled data of 2 Phase 2 clinical studies (CLIN3102 and CLIN3103), a mean difference of –0.8 was observed between difelikefalin and placebo group with an SD of 2.15 and 1.99 in the difelikefalin and placebo group, respectively, regarding the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at end of Week 4.

Based on the results observed at the end of Week 4 in previous studies as mentioned in the above paragraphs, a mean difference of −0.9 with a common SD of 2.1 is assumed between difelikefalin and placebo group regarding the primary endpoint. Assuming a 2-sided significance level of 5% and a statistical power of 90%, 116 subjects per group will be required to detect a difference of −0.9, with a common SD of 2.1, between the difelikefalin and the placebo group using a 2-sample t-test. In addition, assuming, a 10% drop out rate, 258 subjects in total need to be enrolled in the double-blind study period, i.e., 129 subjects per group.

The sample size calculation was done with the software nQuery Version 8.6 using a 2-sample t-test to compare means.

Open-label Extension Period

All subjects who completed the double-blind period may continue into the 14-week open-label extension period if they meet the eligibility criteria at Day 1 of the open-label extension period.

12.3 Randomisation

All subjects enrolled must be identifiable throughout the study.

Randomisation of subjects will be performed on Day 1 before start of treatment with study drug.

Each eligible subject will be randomised during the double-blind period in a 1:1 allocation ratio to receive either difelikefalin or matching placebo using a validated centralised procedure (IWRS) that automates the random assignment of treatment groups to randomisation numbers. Subjects will be stratified according to their use or non-use of concomitant medications to treat their itch (refer to Section 6.8.1) during the week prior to randomisation (run-in period) as well as the presence or absence of specific medical conditions. These specific medical conditions include:

- History of fall or fracture (related to fall)
- Confusional state or mental status change or altered mental status or disorientation
- Gait disturbance or movement disorder

Randomised subjects who terminate their study participation for any reason regardless of whether the investigational product was taken or not, will retain their randomisation number. The next subject will be given the next randomisation number.

Before the start of the study, a randomisation list will be created for each stratum. The randomisation lists will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding.

12.4 Analysis Populations

12.4.1 Double-blind Safety Analysis Set

The DB-SAF consists of all randomised subjects who receive at least 1 dose of investigational product during the double-blind period. Subjects in the DB-SAF will be analysed according to the actual treatment received. The DB-SAF will be used to analyse exposure data as well as all safety endpoints collected during the double-blind period.

12.4.2 Full Analysis Set

The FAS is defined as all subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least 1 dose of investigational product
- Had a non-missing baseline assessment for the weekly mean of the daily 24-hour WI-NRS score

- Had at least 1 post-baseline assessment for the weekly mean of the daily 24-hour WI-NRS score

Subjects in the FAS will be analysed according to their randomised treatment, regardless of the actual treatment received. The FAS will be used to analyse all efficacy endpoints collected during the double-blind period.

12.4.3 Per-Protocol Set

The PPS consists of all subjects who, in addition to the FAS criteria, do not have any major protocol deviations that will be defined and reviewed during the blinded data review meeting prior to unblinding the data. Subjects in the PPS will be analysed according to their randomised treatment, regardless of the actual treatment received. The PPS will be used to analyse efficacy endpoints collected during the double-blind period and will act as supportive analyses.

12.4.4 Open-label Safety Analysis Set

The OL-SAF consists of all subjects who receive at least 1 dose of investigational product in the open-label extension period. Subjects in the OL-SAF will be analysed according to the actual treatment sequence received during the double-blind and open-label extension periods. The OL-SAF will be used to analyse exposure data to difelikefalin, efficacy as well as all safety endpoints collected during the open-label extension period.

12.5 Background and Demographic Characteristics

For the double-blind period, the number of subjects enrolled, randomised, treated, completed, or discontinued from the treatment and from the study, along with the reason for discontinuation, will be summarised by treatment group and overall.

In addition, the number of subjects in each analysis set will be tabulated.

Subject demographics and baseline characteristics will be summarised by treatment group and overall using descriptive statistics; no formal statistical analysis tests will be performed.

Demographic variables to be summarised will include sex, race, age (years) at informed consent as continuous and categorical variable (18 to <65, ≥65 to <85, ≥85 years) and baseline prescription dry body weight (kg). Height will not be collected.

Baseline characteristics of the disease will also be summarised by treatment group and overall and will include variables such as baseline weekly mean of the daily 24-hour WI-NRS score, use/non-use of anti-itch medication, presence/absence of specific medical conditions, aetiology of CKD, duration of pruritus (years), and years on HD.

Medical history data will be coded using MedDRA and summarised by MedDRA SOC, PT, and treatment group. The data will also be listed, including the verbatim Investigator

description of the relevant medical condition, the coded terms (SOC, PT), start date, end date, and whether or not the condition is ongoing.

12.6 Exposure to Investigational Product

For this study, the duration of double-blind period for each individual subject may be up to 12 weeks, for a total of approximately 36 doses of investigational product administered immediately following each dialysis session. Day 1 of the double-blind period will be defined as the day of administration of the first dose of investigational product. The last day of the double-blind period will be defined as the day of the dialysis session immediately following the last injection of investigational product.

Exposure and treatment compliance during the double-blind period will be summarised by treatment group and by the following parameters:

- Duration of double-blind treatment (days)
- Total number of doses actually received
- Total number of dialysis visits logged
- Number of missed doses
- Number of missed dialysis visits
- Number of subjects with extra doses
- Number of subjects with extra dialysis visits
- Compliance (%)

Duration of double-blind treatment (days) = (date of first dialysis after last dose) – (date of first dose) + 1.

Compliance (%)=actual doses/planned doses

If a subject receives additional dialysis during a given week for any reason, an additional dose of investigational product will be administered following dialysis. A maximum of 4 doses per week is allowed. No additional doses will be given for subjects receiving an additional unscheduled ultrafiltration treatment. The number of subjects getting extra doses will be summarised.

12.7 Concomitant Therapy

All medications will be coded using the World Health Organization Drug Dictionary. Counts and percentages of subject use for each concomitant medication will be tabulated separately by study period, by appropriate World Health Organization Drug Dictionary

classifications and by treatment group. Prior medications will be presented in a listing only. Traditional Chinese medicines should also be recorded.

In addition, prior and concomitant antipruritic medications will be summarised separately by study period; summaries will be presented by ingredient rather than by Anatomical Therapeutic Chemical codes.

A prior medication is defined as any medication taken any time with an end date before the date of the first administration of investigational product.

A concomitant medication is defined as any medication/therapy used on or after the date of the first dose administration of investigational product or as any medication/therapy with a missing end date. If missing, the medication will be assumed to be ongoing and considered as concomitant.

12.8 Efficacy Evaluations

12.8.1 Primary Efficacy Evaluations

The primary efficacy endpoint is defined as the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 (Days 23 to 29) of the double-blind period. The FAS will be used as the primary population for the analysis of the primary efficacy endpoint as well as for its sensitivity analysis. The PPS will be used as a secondary population.

The weekly mean of the 24-hour WI-NRS score will be defined as the sum of the daily WI-NRS score reported during a specific week during the double-blind period (e.g., Days 2 to 8, Days 9 to 15, Days 16 to 22, Days 23 to 29) divided by the number of days with non-missing scores for that week. If the daily WI-NRS is missing for >3 days during a specific week, the corresponding weekly mean WI-NRS will be set to missing. The baseline score will be defined as the average of the daily 24-hour WI-NRS scores collected over the run-in period, including pre-randomisation assessments collected on Day 1.

The change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 (Days 23 to 29) of the double-blind period will be analysed using a MMRM. Missing scores will not be imputed. Assuming that the data are MAR, the estimates of the treatment differences calculated from the MMRM described below are unbiased. The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline NRS score, use of prior anti-itch medication and presence of specific medical conditions as covariates.

Repeated measures will include values collected at the end of Weeks 1, 2, 3, and 4.

An unstructured covariance matrix will be used to model the within-subject errors. Should the model fail to converge, a compound symmetric covariance matrix will be used instead.

The Kenward-Roger2 approximation will be used to estimate the denominator degrees of freedom.

Standard descriptive statistics will be reported on the values and changes from baseline at Week 4 of the double-blind period along with the adjusted mean change at Week 4 for each group and its 2-sided 95% CI. The adjusted mean treatment difference in the change between difelikefalin and placebo groups will be estimated at Week 4 of the double-blind period as the simple contrast in the treatment effect. Its 2-sided 95% CI as well as its p-value will be presented

Testing of the primary efficacy endpoint will be 2-sided and conducted at the 5% error level. The null hypothesis in this study is that there is no treatment difference in the primary efficacy analysis of the primary endpoint, i.e., the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period. The alternative hypothesis is that subjects randomised to difelikefalin experience significantly less itching compared to subjects randomised to placebo.

In the primary efficacy analysis, missing NRS data will not be imputed.

Sensitivity analyses of the primary efficacy endpoint will be conducted to evaluate the robustness of study results under different assumptions and imputation algorithms.

For both sensitivity analyses described below, the adjusted mean change at Week 4 for each group and its 2-sided 95% CI, the adjusted mean treatment difference in the change between difelikefalin and placebo groups at Week 4 of the double-blind period, its 2-sided 95% CI as well as its p-value will be estimated as in the primary efficacy analysis.

Sensitivity 1: Multiple Imputation (MI) – MMRM

Multiple imputed data will be generated using the approach described below. Each imputation data will be analysed using the same MMRM model as the one used for the primary efficacy analysis, and the results of the analyses will be combined. Imputation will be performed using all available data collected at each time point between Week 1 and Week 4 of the double-blind period.

- Intermittent missing NRS scores will first be imputed using the Markov Chain Monte Carlo method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.

- The monotone missing NRS values will then be multiply imputed with the SAS MI procedure using the monotone regression method.

- For each stage, MI will be performed within treatment group with covariates for baseline NRS score, both randomisation stratification factors and all non-missing NRS scores for each week. Should convergence issues occur due to small cell size for the categorical covariates corresponding to strata (at either stage), those specific covariates will be removed from the model.

Sensitivity 2: Placebo MI – MMRM

Multiple imputed data will be generated using the approach described below. Each imputation data will be analysed using the same MMRM model as the one used for the primary efficacy analysis, and the results of the analyses will be combined. Imputation will be performed using all available data collected at each time point between Week 1 and Week 4 of the double-blind period.

- Intermittent missing NRS scores will first be imputed using the Markov Chain Monte Carlo method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data. Covariates for baseline NRS score, both randomisation stratification factors and all non-missing NRS scores for each week will be included.

- The monotone missing NRS values will then be multiply imputed with the SAS MI procedure using the monotone regression method. Covariates for baseline NRS score, both randomisation stratification factors and all non-missing NRS scores for each week will be included.

- The MNAR option in Proc MI will be used with the visit values and will reference the placebo group for informing the imputation.

- For each stage, should convergence issues occur due to small cell size for the categorical covariates corresponding to strata, those specific covariates will be removed from the model.

12.8.2 Secondary Efficacy Evaluations

Secondary and other efficacy endpoints will be analysed using the FAS, as the primary population, and PPS, as a secondary population.

Significance level is set at an alpha of 0.05 (2-sided) and no adjustment will be made for testing multiple secondary outcomes. Some significant findings are expected to occur by chance so undue consideration will not be given to any particular significant difference. Moreover, interpretation of the results will be based on patterns of differences and in conjunction with the results of the primary analyses.

The proportion of subjects achieving ≥3-point and ≥4-point improvement, respectively, from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4, 8 and 12 of the double-blind period will be analysed using a logistic regression model containing terms for treatment group, baseline WI-NRS score, use of prior anti-itch

medication, and presence of specific medical conditions. Missing NRS data will be imputed using a MI approach, assuming that subjects who discontinue double-blind period early would have similar WI-NRS scores as other subjects in their respective treatment arm that have complete data. The observed number and proportion of subjects with ≥3-point and ≥4-point improvement, respectively, among the non-imputed data will be reported along with the imputed data logistic regression model-based estimates of the proportions of responders (as defined above) with their 2-sided 95% CIs, odds ratio as well as 2-sided Wald 95% CIs and p-value. A sensitivity analysis will be performed. The same logistic regression model will be used as the one specified above; the only difference is that subjects who discontinue investigational product early will be considered non-responders. Further details will be specified in the SAP.

Change from baseline in itch-related QoL at end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score will be analysed using a MMRM. Missing scores will not be imputed. Assuming that the data are MAR, the estimates of the treatment differences calculated from the MMRM described below are unbiased. The model will contain treatment, week, and treatment-by-week interaction as fixed effects; baseline score, use of prior anti-itch medication and presence of specific medical conditions as covariates. The baseline 5-D total score will be defined as the value collected on Day 1, prior to randomisation. Repeated measures will include values collected at each time point of the double-blind period. An unstructured covariance matrix will be used to model the within-subject errors. Should the model fail to converge, a compound symmetric covariance matrix will be used instead. The Kenward-Roger2 approximation will be used to estimate the denominator degrees of freedom. Standard descriptive statistics will be reported on the values and changes from baseline at end of Week 12 along with the adjusted mean at end of Week 12 for each group and its 2-sided 95% CI. The adjusted mean treatment difference between difelikefalin and placebo groups will be estimated at end of Week 12 of the double-blind period as the simple contrast in the treatment effect as well as its 2-sided 95% CI and its p-value.

Change from baseline in itch-related QoL at end of Week 12 of the double-blind period, as assessed by the Skindex-10 scale total score will be analysed using the same approach as described above fitted for the change from baseline in itch-related QoL at end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score. The baseline Skindex-10 scale total score will be defined as the value collected on Day 1, prior to randomisation.

Change from baseline in the weekly mean of the 24-hour WI-NRS score at each week of the double-blind period will be analysed following a methodology similar to the one employed for the primary analysis of the primary efficacy endpoint. Repeated measures will include values collected at the end of each week from Week 1 until Week 12 of the double-blind period.

Change from baseline in itch-related QoL at each time point of the double-blind period and of the open-label extension period, as assessed by the Skindex-10 scale total score will be

analysed using the same approach as described above fitted for the change from baseline in itch-related QoL at end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score. Repeated measures will include all values collected during each period separately.

Change from baseline in itch-related QoL at each time point of the double-blind period and of the open-label extension period, as assessed by the 5-D itch scale total score will be analysed separately using the same approach as described above fitted for the change from baseline in itch-related QoL at end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score. Repeated measures will include all values collected during each period separately.

The number and percentage of subjects for each response of the Patient Global Impression of Change will be reported as well as the count of subjects with missing values. The number and percentage of subjects who rate their itch condition as "Very much improved" or "Much Improved" at the end of Week 12 of the double-blind period/end of double-blind will be reported together. The Mantel-Haenszel estimate, adjusting for the randomisation stratification variables, of common odds ratio with its 2-sided 95% CI will be reported. Additionally, the 2-sided exact Clopper Pearson 95% CI for the proportion of subjects who rate their itch condition as "Very much improved" or "Much Improved" will be presented.

12.9 Safety Evaluations

The objective of the evaluation of the safety variables is to investigate the data for any effects on clinical tolerability and laboratory safety variables. All such variables will be summarised by treatment group and by study period (and time point as appropriate). No inferential statistics are planned. Safety data will be summarised descriptively.

12.9.1 Adverse Events

All AEs and pre-treatment AEs will be coded using MedDRA to MedDRA SOC and PT for standardisation and summary purposes.

All reported AEs will be included in summary tables by treatment group and by study period, as appropriate. AEs will also be presented in by-subject AE listings.

AEs relative to the double-blind period are identified as any AE:

- With an onset date after the first dose of the investigational product in the double-blind period for subjects who do not enter the open-label extension period.

- With an onset date after the first dose of the investigational product in the double-blind period up to the first dose of difelikefalin in the open-label extension period for subjects who continue into the open-label extension period.

AEs relative to the open-label extension period are identified as any AE with an onset date after the first dose of difelikefalin in the open-label extension period.

A pre-treatment AE is defined as any AE that has an onset before the first investigational product administration.

The number and percentage of subjects experiencing AEs will be summarised by treatment group and by study period. A subject will be counted only once in the incidence count for a MedDRA SOC or PT, although a subject may have multiple occurrences (start and stop) of an event associated with a specific MedDRA SOC or PT.

The incidence and percentage of subjects experiencing treatment-emergent SAEs and AEs leading to investigational product discontinuation will be presented by the appropriate MedDRA SOC and PT.

AEs will also be summarised by severity and by relationship to investigational product for each study period. If the severity and/or relationship to the investigational product of an AE is missing, a worst-case scenario will be assumed (i.e., the AE will be categorised as "severe" and/or "related" to the investigational product). If a subject reports the same AE multiple times the event with the worst severity and the strongest relationship to investigational product will be tabulated.

For each study period, an overall summary table will be provided, presenting for each treatment group, the number and percentage of subjects as well as the number of events for AEs, SAEs, treatment-emergent deaths, treatment-related AEs, treatment-related SAEs, severe AEs, AEs leading to investigational product interruption, AEs leading to investigational product discontinuation and AESIs.

In addition, the following summary tables will be presented and will include the number and percentage of subjects as well as the number of events for:

- AEs by SOC and PT
- SAEs by SOC and PT
- AEs by SOC, PT, and maximum severity
- Related AEs by SOC and PT
- AEs leading to investigational product discontinuation by SOC and PT
- Most common AEs (≥2% or more of subjects in any treatment group) by PT
- AESIs by PT
- Related AESIs by PT

All AEs will be listed in chronological order, including information such as treatment group/treatment sequence, subject identifier, age, sex, use/non-use of anti-itch medication,

presence/absence of specific medical conditions a flag indicating whether the AE was relative to the double-blind or to the open-label extension period, and all related AE status information (start and stop dates, whether the event was ongoing, study day of onset, severity, seriousness, relationship to study medication, action taken with study treatment, and outcome). Separate listings will be generated for SAEs, deaths, AEs leading to investigational product discontinuation, and pre-treatment AEs. Pre-treatment AEs will not be included in any summary tables.

12.9.2 Special Situations

All special situations will be coded using MedDRA (when applicable). All reported special situations will be included in a by-subject listing.

12.9.3 Vital Signs

For each study period, summary tables for vital signs will include descriptive statistics for baseline and each post-baseline assessment. Descriptive statistics will be calculated on both the actual values and the change from baseline. Baseline is defined as the last measurement taken on or prior to the first day of dosing for each study period. Note that the Day 1 assessment can be included in the evaluation of baseline if that the assessment is performed prior to dosing.

All vital signs will be listed in by-subject listings, including information such as visit, collection date, and will be sorted by subject identifier and date of assessment.

12.9.4 12-lead ECG

For each study period, baseline and change from baseline in ECG parameters will be summarised at each time point.

All 12-lead ECG data will be listed in a by-subject listing.

12.9.5 Physical Examination

Not applicable as physical examination finding will be recorded through medical history or AEs if clinically relevant.

12.9.6 Clinical Laboratory Tests

For each study period, summaries of actual values and the change from baseline to each time point (when applicable) will be presented for quantitative laboratory parameters.

Laboratory values will be reported in Système International units.

Laboratory test results will be classified according to whether the value was below (L), within (N), or above (H) the laboratory parameter reference range. A summary of treatment-emergent shifts will compare the baseline L/N/H classification for each laboratory test to the L/N/H classification at end of the treatment for each study period. For

serum potassium, shift table comparing the baseline L/N/H classification to each post-baseline L/N/H classification will also be provided.

12.10 Interim Analyses

An interim analysis may be performed. Details will be defined in the SAP.

12.11 Handling of Missing Data

Procedures for managing missing data, imputation for missing or partially missing data will be provided in the SAP.

Definitions of baseline will be specified in the SAP and will include rules for identification of baseline values when assessments are missing at the scheduled baseline visit.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [21], and the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) [22] as amended. The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number, and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of the Sponsor.

13.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, regulatory and legal requirements of China, and ICH guidelines; and must have been approved by the IEC prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing. If applicable, consent from female partners (who become pregnant during the study) of male subjects will also be acquired.

13.3 Independent Ethics Committee

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IEC must be submitted by the Investigator for review and approval to the IEC. The Investigator must also ensure that the IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter must be forwarded to the Sponsor before the study is implemented.

Approval by the Human Genetics Resources Administration of China will be obtained prior to study initiating for the different study sites.

13.4 Insurance

The Sponsor confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by Sponsor products used in clinical studies. Insurance coverage is not

extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators and that are not in accordance with accepted common medical practices (lege artis procedures). The Sponsor will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the investigational product or failure to follow the Investigator's instructions.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study-related documents and reports will be available, and that the provision of direct access for monitoring and auditing by the Sponsor or its designees will be permitted. In addition, the Investigator must ensure that all trial related site source data, study-related documents and reports will be made available for Sponsor audit and inspection by the appropriate Regulatory Authority and review by the IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (double-data entry or EDC) into the study database. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, the Sponsor or its designates may review data as deemed necessary.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or
- Investigator site initiation
- Routine site monitoring
- Documented protocol and GCP training
- eCRF and query review against source documents
- Collection of local laboratory normal ranges

14.1 Quality Management: Critical Processes and Data

The following processes and data have been identified during the risk management activities for this trial as critical to ensure human subject protection and the reliability of trial results.

The Sponsor and its designees will ensure a close oversight of the site's activities related to the trial. Throughout the study, the clinical study team will work to ensure that the trial is operationally feasible and focuses on study activities essential to human subject protection and the reliability of trial results, including (but not limited to):

- Study protocol design and implementation
- Tools and procedures supporting data collection and processing

- Tools and procedures safeguarding the rights and protection of human subjects
- Activities essential to trial decision-making and compliance

15. REPORTING AND RECORDING OF DATA

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

15.1.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- The medical history
- The basic identifying information, such as demographics, that link the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs and pregnancies
- All special situations as defined in Section 10.8.1
- The subject's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the subject throughout the study
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation

All data for the study must be available in source documentation.

15.1.2 Records Retention

The Investigator must arrange for the retention of all study documentation (such as eCRF files or printed forms, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer. The Sponsor will inform the Investigator in writing when files can be destroyed.

Archived data may be held on DVD, USB or through a secure file transfer protocol site, or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform the Sponsor immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

15.1.3 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Sponsor Medical Expert as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol (see Section 16.2). The criteria describing protocol deviation(s) and how they will be handled will be documented in the SAP.

16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the Sponsor. Each applicable Regulatory Authority/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The Sponsor is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [23]. The Clinical Trial Agreement describes the Sponsor's publication terms.

Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Vifor Fresenius Medical Care Renal Pharma Ltd. before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria for authorship [24]. That is, all authors must meet each of the following 4 criteria:

1. Substantial contribution to the conception and design of the work; or the acquisition, analysis, or interpretation of data for the work; and

2. Drafting the work or revising it critically for important intellectual content; and

3. Final approved of the version to be published; and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition, certain Sponsor employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

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Appendix 1 Worst Itching Intensity-Numerical Rating Scale

WORST ITCHING INTENSITY
NUMERICAL RATING SCALE (NRS)

SUBJECT NUMBER: ☐☐☐ - ☐☐☐☐

Completed in Dialysis Unit or at Home? **(please mark only one)**

☐ **Dialysis Unit**

☐ **Home**

INSTRUCTIONS

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours by marking the box with the number that best describes it. After completing the scale below, please provide your initials in the **SUBJECT INITIALS** box indicating that you completed the scale by yourself and the **DATE** and **TIME** you completed the scale.

Worst Itching Over the Past 24 Hours

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

NO ITCHING — **WORST ITCHING IMAGINABLE**

Date Completed:

☐☐ ☐☐☐ 2 0 ☐☐

D D M M M Y Y Y Y

Time:

☐☐ : ☐☐

☐ AM ☐ PM

SUBJECT INITIALS

First *Middle* *Last*

☐ ☐ ☐

Note: Section to be completed by the site staff after form has been collected from subject

STUDY DAY NUMBER: ☐

Site Staff Initials:

Appendix 2 New York Heart Association Classification of Heart Failure

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 3 Skindex-10 Scale

SKINDEX-10 QUESTIONNAIRE

SUBJECT NUMBER: ☐☐☐ - ☐☐☐☐

INSTRUCTIONS: During the past **WEEK**, how often have you been bothered by:							
	0 (Never bothered)	**1**	**2**	**3**	**4**	**5**	**6** (Always bothered)
1. Your itching	☐	☐	☐	☐	☐	☐	☐
2. The persistence/reoccurrence of your itching	☐	☐	☐	☐	☐	☐	☐
3. The appearance of your skin from scratching	☐	☐	☐	☐	☐	☐	☐
4. Frustration about your itching	☐	☐	☐	☐	☐	☐	☐
5. Being annoyed about your itching	☐	☐	☐	☐	☐	☐	☐
6. Feeling depressed about your itching	☐	☐	☐	☐	☐	☐	☐
7. Feeling embarrassed about your itching	☐	☐	☐	☐	☐	☐	☐
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	☐	☐	☐	☐	☐	☐	☐
9. The effects of your itching on your desire to be with people	☐	☐	☐	☐	☐	☐	☐
10. The effect of your itching making it hard to work or do what you enjoy	☐	☐	☐	☐	☐	☐	☐

Date Completed: ☐☐ ☐☐☐ 2 0 ☐☐
D D M M M Y Y Y Y

Time: ☐☐ : ☐☐
☐ AM ☐ PM

SUBJECT INITIALS *First Middle Last*
☐ ☐ ☐

Note: Section to be completed by the site staff after form has been collected from subject

STUDY DAY NUMBER: ☐

Site Staff Initials:

- Patient Related Outcome (PRO) Worksheet Version 1.0 , 10 Oct 2017 Page 1 of 1

Appendix 4 5-D Itch Scale

1.	DURATION:	During the last 2 weeks, how many hours a day have you been itching?				
		Less than 6 hrs/day	6-12 hrs/ day	12-18 hrs/day	18-23 hrs/day	All day
		☐	☐	☐	☐	☐
2.	DEGREE:	Please rate the intensity of your itching over the past 2 weeks				
		Not present	Mild	Moderate	Severe	Unbearable
		☐	☐	☐	☐	☐
3.	DIRECTION:	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?				
		Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting Worse
		☐	☐	☐	☐	☐
4.	DISABILITY:	Rate the impact of your itching on the following activities over the last 2 weeks				
	Sleep	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
		☐	☐	☐	☐	☐
		N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
	Leisure/Social	☐	☐	☐	☐	☐	☐
	Housework/ Errands	☐	☐	☐	☐	☐	☐
	Work/School	☐	☐	☐	☐	☐	☐

5.	DISTRIBUTION:	Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.			
		Head/Scalp	☐	Soles	☐
		Face	☐	Palms	☐
		Chest	☐	Tops of Hands/Fingers	☐
		Abdomen	☐	Forearms	☐
		Back	☐	Upper Arms	☐
		Buttocks	☐	Points of Contact w/ Clothing (e.g., waistband, undergarment)	☐
		Thighs	☐		
		Lower legs	☐	Groin	☐
		Tops of Feet/Toes	☐		

Appendix 5 Patient Global Impression Change

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved

[2] ☐ Much Improved

[3] ☐ Minimally Improved

[4] ☐ No Change

[5] ☐ Minimally Worse

[6] ☐ Much Worse

[7] ☐ Very Much Worse